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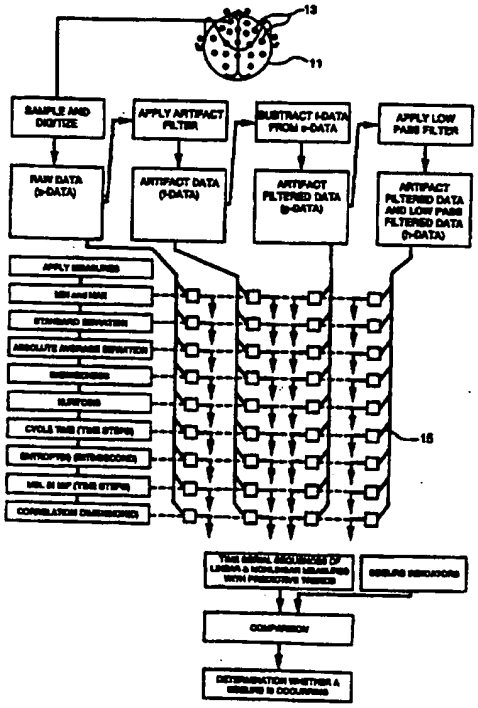
(54) Title: EPILEPTIC SEIZURE DETECTION BY NONLINEAR METHODS

(57) Abstract

Methods and apparatus for automatically detecting epileptic seizures by monitoring and analyzing brain wave (EEG or MEG) signals of a patient (11) using EEG electrodes (13). Steps include: acquiring the brain wave data from the patient; digitizing the data; obtaining nonlinear measures (15) of the data via chaotic time series analysis; obtaining time serial trends in the nonlinear measures; determining that one or more trends in the nonlinear measures indicate a seizure, and providing notification of seizure occurrence.



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EPILEPTIC SEIZURE DETECTION BY NON-LINEAR METHODS

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FIELD OF THE INVENTION

The present invention relates to the application of chaotic time series analysis (CTSA) to electroencephalogram (EEG) data and magnetoencephalogram (MEG) data, and more particularly to the analysis of the data to detect epileptic seizures.

CROSS-REFERENCE TO RELATED APPLICATIONS

This invention is related to Docket No. 1743-X Epileptic Seizure Prediction by Non-linear Methods by Lee M. Hively, Ned E. Clapp, C. Stuart Daw, and William F. Lawkins and to Docket No. 1744-X Method and Apparatus for Extraction of Low-Frequency Artifacts from Brain Waves for Alertness Detection by Ned E. Clapp and Lee M. Hively, both of which are filed on even date herewith, and both of which are assigned to the same entity.

BACKGROUND OF THE INVENTION

The theory of nonlinear dynamics provides a basis for understanding and potentially controlling many complex physical and engineering systems. An extensive literature exists for nonlinear dynamics in the brain and related work (18). It is well known that brain waves exhibit seemingly random, unpredictable behavior, that is characteristic of deterministic chaos (1, 20). Moreover, chaotic behavior is "normal," while nonchaotic or periodic behavior is indicative of pathophysiology in experimental epilepsy (20). Schiff et al. (11) showed that chemically-induced seizures in rat-brain can be electrically controlled, leading to speculation (4) that human

epilepsy may be controlled without drug or surgical intervention. However, effective use of chaos control for epilepsy requires definitive seizure detection. Thus, this invention diagnoses brain wave data via chaotic time series analysis (CTSA) methods to detect an epileptic seizure.

Nonlinear analysis of neurological diseases via EEG data is extensive. For example, see the 1994 review by Elbert et al. (18). Epilepsy can be recognized only with clear EEG manifestations, but even these seizures are not easy to detect because there is no stereotyped pattern characteristic of all seizures (5). Work by Olsen and colleagues (7) used various linear measures with autoregressive modeling, discriminant analysis, clustering, and artificial neural networks. Valuable nonlinear tools for studying EEG data include correlation dimension, mutual information function, Kolmogorov entropy, phase-space attractors, and largest Lyapunov exponent.

Very recent analysis by Theiler (16) studied correlation dimension and Lyapunov exponent, using a form of surrogate analysis on a single EEG time series during an epileptic seizure. The surrogate analysis involved a random shuffling of blocks of time serial data, each block containing one quasi-periodic spike-wave complex. The auto-correlation function for the original data is nearly indistinguishable from the surrogate data. The correlation dimension for the original data is significantly different from the surrogate data only at large scale sizes and large embedding dimensions. The maximum Lyapunov exponent (λ) was negative for both the original and surrogate data and not substantially different, contrary to previous work which found positive λ values. Theiler concluded that his analysis suggests a nonlinear oscillator with noise on the time scale of the spike-wave complex, but cannot indicate whether chaos exists on a shorter time scale.

Other patents for epileptic seizure detection have been granted. U. S. Patent No. 5,311,876 "Automatic Detection of Seizures Using Electroencephalograpic Signals" by D. E. Olson et al. relies on linear analysis of EEG features for seizure detection. U. S. Patent No. 5,349,962 "Method and Apparatus for Detecting Epileptic Seizures" by J. S. Lockard et al. detects seizures if the wavefom is within a predetermined threshold. These patents use linear

methods, as distinguished from the nonlinear techniques of the present invention. No other work is known that applies several CTSA measures to EEG data or MEG data for systematic characterization of non-seizure, seizure, and transition-to-seizure.

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OBJECTS OF THE INVENTION

Accordingly, it is an object of the present invention to provide new and improved methods and apparatus for detecting epileptic seizures in a patient and providing notification to

permit assistance to be given to the patient or to a person who can assist the patient.

Further and other objects of the present invention will become apparent from the description contained herein.

SUMMARY OF THE INVENTION

In accordance with one aspect of the present invention, the foregoing and other objects are achieved by a method for automatically detecting an epileptic seizure in a patient comprising the steps of: providing at least one channel of a patient's raw brain wave data, called e-data, selected from the group consisting of electroencephalogram data and magnetoencephalogram data; separating the e-data into artifact data, called f-data, and artifict-free data, called g-data, while preventing phase distortions in the data; processing g-data through a low-pass filter to produce a low-pass-filtered version of g-data, called h-data; applying at least one nonlinear measure selected from the group consisting of time steps per cycle, Kolmogorov entropy, first minimum in the mutual information function, and correlation dimension to at least one type of data selected from the group consisting of e-data, f-data, g-data, and h-data to provide at least one time serial sequence of nonlinear measures, from which at least one indicative trend selected from the group consisting of abrupt increases and abrupt decreases can be determined; comparing at least one indicative trend with at least one known seizure indicator; and determining from said comparison whether an epileptic seizure is occurring in the patient.

In accordance with a second aspect of the present invention, the foregoing and other objects are achieved by apparatus for automatically detecting an epileptic seizure in a patient comprising: data provision means for providing at least one channel of a patient's raw brain wave data called e-data selected from the group consisting of electroencephalogram data and magnetoencephalogram data; separation means for separating e-data into artifact data, called f-data, and artifact-free data, called g-data, while preventing phase distortions in the data, communicably connected to the data provision means; low-pass filter means for filtering g-data to produce a low-pass filtered version of g-data, called h-data, communicably connected to the

separation means; application means for applying at least one nonlinear measure selected from the group consisting of time steps per cycle, Kolmogorov entropy, first minimum in the mutual information function, and correlation dimension to at least one type of data selected from the group consisting of e-data, f-data, g-data, and h-data to provide at least one time serial sequence of nonlinear measures, from which at least one indicative trend selected from the group consisting of abrupt increases and abrupt decreases can be determined, communicably connected to the low-pass filter means; comparison means for comparing at least one indicative trend with known siezure indicators, communicably connected to the application means; and determination means for determining from the comparison whether an epileptic seizure is occurring in the patient, communicably connected to the comparison means.

BRIEF DESCRIPTION OF THE DRAWINGS

In the drawings:

Fig. 1 is a block diagram showing how, in accordance with the present invention, EEG data is obtained from the patient, digitized, processed, and analyzed by nonlinear methods to detect and/or predict epileptic seizures.

Fig. 2 shows standard EEG electrode positions on a patient's scalp for the bipolar montage, looking from above.

Fig. 3 shows sample plots of EEG data, to illustrate raw data (e-data as the dotted curve in fig. 3a), and artifact-filtered data (g-data, shown in fig. 3b), as an example of the method and apparatus of this invention.

Fig. 4 comprises Figs. 4.1, 4.2, 4.3, and 4.4, and shows linear and nonlinear measures of time serial data for Example I. 4.1 shows linear and nonlinear measures of raw (e-data); 4.2 shows linear and nonlinear measures of artifact (f-data); 4.3 shows linear and nonlinear measures of artifact-filtered (g-data); and 4.4 shows linear and nonlinear measures of artifact- and low-pass filtered (h-data). Various mathematical properties and characteristics are shown for each data type, and are further shown in parts (a), (b), (c), (d), (e), (f), (g), (h), and (i) for each data type.

These measures are shown as curves, each curve representing a time serial sequence of linear or nonlinear measures. Within each curve, significant features such as abrupt increases and abrupt decreases may be viewed as indicative trends which are then compared to to trends which have been shown to be siezure indicators. Thus from the comparison it can be determined whether a siezure is occurring in the patient. In parts (a), (b), (c), (d), and (e) for each data type, the solid line is the specific measure, the dashed line is the 11-point average, and the dotted line is the standard deviation for the measure.

Fig. 5 comprises Figs. 5.1, 5.2, 5.3, and 5.4, and shows linear and nonlinear measures of time serial data for Example II. 5.1 shows linear and nonlinear measures of raw (e-data); 5.2 shows linear and nonlinear measures of artifact EEG (f-data); 5.3 shows linear and nonlinear measures of artifact-filtered (g-data); and 5.4 shows linear and nonlinear measures of artifact- and low-pass filtered (h-data). Various mathematical properties and characteristics as computed for each data type are further shown in parts (a), (b), (c), (d), (e), (f), (g), (h), and (i) for each data type. These measures are shown as curves, each curve representing a time serial sequence of linear or nonlinear measures. Within each curve, significant features such as abrupt increases and abrupt decreases may be viewed as indicative trends which are then compared to to trends which have been shown to be siezure indicators. Thus from the comparison it can be determined whether a siezure is occurring in the patient. In parts (a), (b), (c), (d), and (e) for each data type, the solid line is the specific measure, the dashed line is the 11-point average, and the dotted line is the standard deviation for the measure.

For a better understanding of the present invention, together with other and further objects, advantages and capabilities thereof, reference is made to the following disclosure and appended claims in connection with the above-described drawings.

DETAILED DESCRIPTION OF THE INVENTION

Chaotic time series analysis (CTSA) is applied to human electroencephalogram (EEG) data.

For reference, equation numbers are shown at the right of each equation.

Three epochs were examined: epileptic seizure, non-seizure, and transition from non-seizure to seizure. The CTSA tools were applied to four forms of these data: raw EEG data (e-data), artifact data (f-data) via application of a quadratic zero-phase filter of the raw data, artifact-filtered data (g-data) that was the residual after subtracting f-data from e-data, and a low-pass-filtered version (h-data) of g-data. Several nonlinear measures uniquely indicate an epileptic seizure, including: an abrupt increase in the number of timesteps per cycle for f-data; an abrupt increase in the number of timesteps per cycle for g-data; an abrupt increase in the number of timesteps per cycle for h-data; an abrupt increase in the entropy of e-data; an abrupt increase in the entropy of f -data; an abrupt increase in the entropy of g-data; an abrupt increase in the entropy of h-data; an abrupt decrease in the first minimum in the mutual information function for f-data; an abrupt decrease in the first minimum in the mutual information function for h-data; an abrupt increase in the correlation dimension of e-data; an abrupt increase in the correlation dimension of f-data; an abrupt increase in the correlation dimension of g-data; an abrupt increase in the correlation dimension of h-data; and combinations thereof. Analysis of e-data shows that statistically significant nonlinear structure is present during the non-seizure, transition, and seizure epochs.

Two sets of channel-13 EEG data from one patient are provided as examples. In Fig. 1 of the drawings, 11 shows the patient's head, looking from above. 13 shows EEG electrode positions on the patient's scalp. 15 shows a nonlinear measure of EEG data. In Fig. 2 of the drawings, C13 labels the position where the channel 13 data, which is used in this work, originates. Analysis of C13 data was chosen for these examples to demonstrate the robust removal of eye-blink artifact, which otherwise dominates channel 13 because of its proximity to the eye. This method and apparatus can be applied to data from other EEG channels, as well as to MEG data, as is apparent to those skilled in the art. Both sets of data included non-seizure, transition-to-seizure, and epileptic seizure data. The analysis included various linear measures (standard deviation, absolute average deviation, skewedness, kurtosis), plus nonlinear measures

(time steps per cycle, Kolmogorov entropy, first minimum in the mutual information function, and correlation dimension). Four forms of the data were analyzed: raw EEG (e) data, artifact (f) data via application of a zero-phase quadratic filter, artifact-filtered (g) data that was the residual after subtracting f-data from g-data, and a low-pass-filtered version (h) of the g-data. The nonlinear measures clearly discerned the epileptic seizures in these examples, while none of the linear measures provided definitive seizure indication. Nonlinear tools identified seizure indicators with and without artifact removal, with and without low-pass filtering, demonstrating the robustness of these methods to noise and artifacts. Surrogate analysis of e-data showed that this data has significant nonlinear structure.

In the examples described herein, sixteen channels of EEG data were analyzed in the bipolar montage, as illustrated in Fig. 2. The data were retrieved in analog form from VHS tapes and converted to digital form with 12-bit precision, giving an integer between -2048 and +2047. The digital sampling rate (f_s) was 512 Hz over a total sample time of 10-23 minutes, corresponding to a total dataset size of 9.8-22.5 megabytes in binary form. Three epochs of data were examined: epileptic seizure and post-seizure, non-seizure, and transition from non-seizure state to seizure (transition).

It is acknowledged that to detect an epileptic seizure as it occurs, the brain wave data used would not be recorded data, but would be currently-occurring data. This data would be taken from the patient to the apparatus directly using standard EEG or MEG methods, or indirectly by transmitting the data to an apparatus remote from the patient by means such as telephone, radio, or other communications means well known to the skilled artisan.

Raw brain wave data contains not only signals associated with brain activity, but also contains artifacts (e.g., eye blinks, muscle twitches, chewing, etc.) that obscure the brain-wave signal. In order to observe artifact-free data and artifact data independently, the raw data must be separated into artifact data and artifact-free data. A zero-phase filter was developed and used to remove low-frequency artifacts, based on the following criterion. A zero-phase-shift filter was needed to prevent phase distortions when subtracting the filter output (the "artifact" data signal)

from the raw data signal to yield an undistorted artifact-filtered or artifact-free data signal, because phase relationships are most important in the subsequent nonlinear analysis. Standard high-pass filter techniques do not meet this criterion. A computationally fast, simple, low-frequency signal follower was necessary to eventually apply the filter in real- or near-real time. Consequently, quadratic regression analysis was used, with the same number of data samples on either side of a central point. Other standard digital filtering methods (15) could not meet this requirement.

The zero-phase filter method and apparatus which may be embodied in various ways well known to one skilled in the art, such as a specially-programmed computer or a programmed integrated circuit, semi-conductort chip, or micro-processor, is as follows. For a specific channel, the EEG signal (e) at time (t) is sampled at regular intervals ($t_i = i\,\Delta t$) to yield a set of time serial data $e_i = e(t_i)$. We choose a filter-window length of $2n + 1$ points from the time series, where n is the number of points on either side of the central point (e_c) as indicated in the sequence below.

central point

$$\underbrace{e_{c-n}, e_{c-n+1}, \cdots, e_{c-1}}_{\text{n points}}, e_c, \underbrace{e_{c+1}, \cdots, e_{c+n-1}, e_{c+n}}_{\text{n points}}$$

The data was fitted to a quadratic equation that takes the form: $F_i = F(t_i) = a_1 (t_i - t_c)^2 + a_2 (t_i - t_c) + a_3 = a_1 T_i^2 + a_2 T_i + a_3$. Here, $t_c = c\,\Delta t$ is the time at the central point, and $T_i = t_i - t_c$. This approximation is fitted to the data, by minimizing the sum of squares of the differences between the quadratic equation, F(t), and the raw EEG data, e(t), corresponding to the minimum in the following function:

$$L = \sum_{i=c-n}^{c+n} [F(t_i) - e(t_i)]^2 = \sum_{i=-n}^{n} [(a_1 T_i^2 + a_2 T_i + a_3) - e_{i+c}]^2 \qquad \text{Eq. 1}$$

The minimum in L is found from the condition $\partial L/\partial a_k = 0$, for $k = \{1, 2, 3\}$, forming three simultaneous linear equations in three unknowns. The window-averaged artifact (F_c) is given by the fitted value of the central point, $F_c = F(0) = a_3$. Note that the sums over odd powers of T_i are zero and that symmetric sums over even powers of T_i (over i from -n to +n) can be converted to sums from 1 to n with $T_i = i\,\Delta t$, yielding a window-averaged solution for the artifact signal:

$$F_c = \frac{3(3n^2+3n-1)(\sum_i e_{i+c}) - 15(\sum_i i^2 e_{i+c})}{(4n^2+4n-3)(2n+1)} \qquad \text{Eq. 2}$$

Here, Σ_i indicates the sum over i from -n to +n. Sums over even powers of "i" were explicitly evaluated with standard formulae (10). The effort to evaluate F_c can be reduced substantially by computing the sums initially from Eq.2 (at c = n + 1), and then using the following recursions thereafter:

$$\sum_{i=-n}^{n} e_{i+c+1} = e_{c+n+1} - e_{c-n} + \sum_{i=-n}^{n} e_{i+c} \qquad \text{Eq. 3}$$

$$\sum_{i=-n}^{n} i e_{i+c+1} = n e_{c+n+1} - (n+1) e_{c-n} + \sum_{i=-n}^{n} i e_{i+c} - \sum_{i=-n}^{n} e_{i+c} \qquad \text{Eq. 4}$$

$$\sum_{i=-n}^{n} i^2 e_{i+c+1} = n^2 e_{c+n+1} - (n+1)^2 e_{c-n} + \sum_{i=-n}^{n} i^2 e_{i+c} - 2\sum_{i=-n}^{n} i e_{i+c} + \sum_{i=-n}^{n} e_{i+c} \qquad \text{Eq. 5}$$

The right-hand sides of Eqs. 3-5 only involve the sums previously computed. Application of Eqs. 2-5 to the N-point set of original time serial EEG data (e_i, illustrated as the

dotted curve in Fig. 3a) yields an artifact dataset (f_i or f-data, illustrated as the solid curve in Fig. 3a) with (N-2n) points that contains the low frequency artifact signal. The residual signal (g_i or g-data, illustrated as the solid curve in Fig. 3b) is the difference, $g_i = e_i - f_i$, and is a signal that is free of low-frequency artifacts. Subsequently, the g-data is processed through a standard fourth-order low-pass filter at 50 Hz (e.g., see Ref. 9) to yield artifact-filtered, low-pass-filtered data (h_i or h -data) that is free of both low- and high-frequency artifacts. Note that spike-wave phenomena at 100 Hz in h-data are attenuated by 28 db (a factor of 25), while the g-data retain the full spike-wave signals. A standard second-order, third-order, or fourth order filter at frequencies between about 35 Hz and about 60 Hz would also be effective as a low-pass filter.

The filter-window length (n=128) corresponds to a frequency of 2.0 Hz [=512 Hz/(2n +1)]. Figure 3a shows an example of the application of this method, with (raw) e-data in light gray and a superimposed (dark line) artifact signal (f-data), which clearly follows the low-frequency trends. Figure 3b shows the residual signal (g-data) for this example, as having little low-frequency component while retaining the higher frequency information.

For a specific EEG channel, a time history of the nonlinear measures was obtained by applying the CTSA tools to a series of 20-second analysis-windows of the four data types (e, f, g, h). These data are designated herein as x_i. The length of the analysis window (w) was 10,240 points. Each analysis-window had a 5,120-point overlap with the previous (or next) analysis-window of data. This 50% overlap provides an optimal mix of new and old data for smooth time-history trend generation (2), as illustrated below.

```
|<---0 to 20 seconds--->|
        |<---10 to 30 seconds--->|
                |<---20 to 40 seconds--->|
                        ...
                          ...
                                |<--100 to 120 seconds-->|
                                        |<--110 to 130 seconds-->|
                                                                ...
                                                                ...
```

The zero-phase quadratic filter provides artifact-filtered data with frequencies of ≥2 Hz. A heuristic for (linear) Fourier analysis is that ≥10 periods of data are required to faithfully recover cyclic information at a specific frequency. Thus, ≥5 seconds of data are needed to obtain Fourier amplitude and phase information at a signal frequency of 2 Hz. However, this heuristic does not apply to nonlinear analysis. For example, 20 seconds of data are necessary to obtain consistent results for the Kolmogorov entropy. This need for longer dataset lengths (~10,000 points) for consistent nonlinear measures conflicts with the need for shorter dataset lengths (≤5,000 points) to provide adequate resolution for the time history generation of trends. Consequently, a 20-second analysis window was used, as described above, with a 50% overlap for an effective time history resolution of 10 seconds. The nonlinear measures for each 20-second analysis window were associated with the time at the center of the analysis window, i.e., every ten seconds. Shorter or longer analysis window lengths can be used in proportion to higher or lower data sampling rates, as is obvious to those skilled in the art.

Many characterization tools exist for chaotic data analysis. A subset of the tools that were found in previous work to be good measures for EEG data were used in carrying out the present invention. These tools include the following: standard statistical measures (minimum, maximum, average, absolute average deviation, standard deviation, skewedness, kurtosis, time per cycle); Kolmogorov entropy and entropy spectrum; mutual information function; maximum likelihood correlation dimension and correlation dimension spectrum; surrogate generation and nonlinearity tests; and nonlinear digital filters (as discussed herein).

Entropy, correlation dimension, and mutual information were used in the present invention as nonlinear measures for seizure analysis. The first minimum in the mutual information defines the time scale for generating the return map for EEG dynamics. The return map underlies the correlation dimension (measure of dynamic complexity) and entropy (measure of dynamic predictability). We have applied these same measures successfully in analyzing other systems.

The statistical measures for the present study are obtained by standard methods (6). The maximum and minimum are obtained as maximum and minimum (respectively) over the x_i values in a time-serial window of w points. The average ($\bar{x}$) is given by:

$$\bar{x} = \left(\frac{1}{w}\right)\sum_{i=1}^{w} x_i \qquad \text{Eq. 6}$$

The r-th order moment (m_r) of the x-data is:

$$m_r = \left(\frac{1}{w}\right)\sum_{i=1}^{w} (x_i - \bar{x})^r \qquad \text{Eq. 7}$$

The absolute average deviation (a) provides a robust indicator of the x_i variability (13) and is defined as:

$$a = \left(\frac{1}{w}\right)\sum_{i=1}^{w} |x_i - \bar{x}| \qquad \text{Eq. 8}$$

An unbiased estimate of the standard deviation (σ) is:

$$\sigma = \left[\frac{w m_2}{w-1}\right]^{1/2} \qquad \text{Eq. 9}$$

An estimate for the skewedness (s) is:

$$s = \frac{m_3}{m_2^{3/2}} \qquad \text{Eq. 10}$$

An estimate for the kurtosis (k) is:

$$k = \frac{m_4}{m_2^2} - 3 \qquad \text{Eq. 11}$$

The average cycle time (T_c) is important as a characteristic time of the nonlinear system:

$$T_c = \frac{window\ length\ in\ timesteps}{\left(\frac{number\ of\ mean\ crossings}{2}\right)} \qquad \text{Eq. 12}$$

The mutual information function (MIF) is a nonlinear version of the (linear) auto-correlation and cross-correlation functions, and was developed by Fraser and Swinney (3). Mutual information measures the certainty with which a measurement can be predicted, given the outcome of another related measurement. Examples of the later include the same EEG channel at a different time, and another EEG channel at the same (or different) time. The MIF indicates the average information (in bits) that can be inferred from one measurement about a second measurement, and is a function of the time delay (number of time steps) between the measurements. The mutual information function also measures the nonlinear time dependent correlation in the same signal. For EEG data, information decay in an individual channel (univariate MIF) indicates local time scale, as the average time lag ($t_j - t_i$) that makes $x(t_i)$ independent of $x(t_j)$, and corresponds to the first (local) minimum (M_1 in timesteps) in the MIF (3). For use herein, a minimum is defined as two successive decreases in the signal value, followed by two successive increases in signal value. Other definitions were tested and found to yield less consistent results. The MIF, I(Q,S), and system entropy (H) for two measurements (Q and S) are defined by:

$$I(Q,S) = I(S,Q) = H(Q) + H(S) - H(S,Q) \qquad \text{Eq. 13}$$

$$H(S) = -\sum_i P_S(s_i)\log[P_S(s_i)] \qquad \text{Eq. 14}$$

$$H(S,Q) = -\sum_{ij} P_{SQ}(s_i,q_j)\log[P_{SQ}(s_i,q_j)] \qquad \text{Eq. 15}$$

S denotes the whole system that consists of a set of possible messages (measurements for the value of s), $s_1, s_2, \ldots, s_n$ with associated probabilities $P_S(s_1), P_S(s_2), \ldots, P_S(s_n)$. Q denotes a second system that consists of a set of possible messages (measured values with a time delay relative to the s_i values), $q_1, q_2, \ldots, q_n$ with associated probabilities $P_Q(q_1), P_Q(q_2), \ldots, P_Q(q_n)$. The function $P_{SQ}(s_i, q_j)$ denotes the joint probability of both states occurring simultaneously. If the logarithm is taken to the base two, then H is in units of bits. Fraser and Swinney (3) describe the details for evaluating I(Q,S), including a sequence of recursive partitions in (s_i, q_j) space to achieve adequate accuracy with tailoring to the local data structure.

The maximum-likelihood correlation dimension (D) is based on the early work by Takens (14) with modifications for noise (13):

$$D = \left[\left(-\frac{1}{M}\right)\sum_{ij} \ln\left(\frac{r_{ij}-r_n}{1-r_n}\right)\right]^{-1} \qquad \text{Eq. 16}$$

where M is the number of randomly sampled point pairs, r_{ij} is the normalized maximum-norm distance between the (randomly chosen) i-j point pairs as defined in Eq. 17 (below), and r_n is the normalized distance (scale length) associated with noise as measured from the time serial data. The distances are normalized with respect to some nominal scale length (L_0), i.e. $r_{ij} = L_{ij}/L_0$ and $r_n = L_n/L_0$ with L_0 as a representative scale length (typically a multiple of the absolute average deviation). The choice of scale length is a balance between a small scale for sensitivity to local dynamics (typically at $L_0 < 5a$) and avoidance of excessive noise (typically at $L_0 \geq a$). The distances (L_{ij}) are defined by:

$$L_{ij} = \max_{0 \le k \le m-1} |x_{i+k} - x_{j+k}| \qquad \text{Eq. 17}$$

where m is the average number of points per cycle from Eq. 12 (i.e., $m = T_c$). Schouten et al. (40) describe the details for evaluating Eqs 16-17 to measure of the number of degrees of freedom in a system (e.g., the number of coupled first-order differential equations to depict the dynamics).

The Kolmogorov entropy (K-entropy or simply entropy) measures the rate of information loss per unit time, or (alternatively) the degree of predictability. A positive, finite entropy generally is considered to be a clear demonstration that the time series and its underlying dynamics are chaotic. An infinite entropy indicates a stochastic, non-deterministic (totally unpredictable) phenomenon. For entropy determination, one begins with two orbits on a chaotic attractor that are initially very close together. The entropy then is estimated from the average divergence time for pairs of initially-close orbits. More precisely, the entropy is obtained from the average time for two points on an attractor to go from an initial separation ($L < L_0$), to become separated by more than a specific distance ($L \ge L_0$). The maximum-likelihood entropy (K):

$$K = -f_s \log\left(1 - \frac{1}{\bar{b}}\right) \qquad \text{and} \qquad \text{Eq. 18}$$

$$\bar{b} = \left(\frac{1}{M}\right)\sum_{i=1}^{M} b_i \qquad \text{Eq. 19}$$

with b_i as the number of timesteps for two points, initially within $L<L_0$, to diverge to $L \ge L_0$. The work by Schouten et al. (12), and references therein, provide details of the method. Note that the

entropy used here is the order-2 Kolmogorov entropy which hereafter is called simply entropy.

The entropy (K) and correlation dimension (D) usually are reported in the limit of zero scale length. However, EEG data (and all biomedical data) have substantial noise. Consequently, the nonlinear measures, K and D, are reported for a finite scale length (L_0) that is slightly larger than the noise. Thus, the values of K and D, that are reported here, do not capture the full complexity of brain dynamics, i.e., their values are smaller than expected for the zero-scale-length limit. K and D are interpreted as nonlinear statistical indices of finite-scale dynamic structure.

EXAMPLE I

The method and apparatus of this invention are illustrated by the analysis of two datasets. Both datasets are from the same patient, who is a 20-year-old female with a lifelong history of seizures, beginning at age 4 months. The cause of the seizures is not established, although neuro-imaging studies (including computerized tomography and magnetic resonance) are normal. The seizures are poorly controlled despite treatment with various combinations of anti-epileptic drugs, which at the time of the recordings were Phenytoin, Phenobarbital, and Felbamate. The seizures are partial complex with some occasions of secondary generalization. During the seizure designated Example I, the patient was sitting up in bed, doing some neurophysiologic testing. Her EEG shows an activated pattern. She then showed automatisms with picking movements and staring, followed by vocalizations (several seconds of screams). Hyper-extended head and neck posturing followed. Her upper extremities became flexed, and then she showed clonic activity, involving abduction/adduction at the shoulders and hips. There was tonic posturing and clonic activity of all extremities. The convulsive movements were associated with high-amplitude EEG waves, involving spikes, polyspikes, and much artifact activity. As the clinical seizure spontaneously terminated, the subject was unresponsive and made loud snoring sounds. Then, the brain wave amplitudes became quite suppressed. The automatisms were associated with polyspike discharges from the left frontal region. After seizure termination,

spike discharges occurred from this same region, followed by suppressed background waves.

The results from Example I involved four analyses (e-, f-, g-, and h-data) on the three epochs of channel 13 data (epileptic seizure and post-seizure, non-seizure, and transition from non-seizure to seizure). These three epochs of data were provided and analyzed as three separate, non-contiguous ten-minute data segments. The non-seizure data segment ended several hours before the transition data, which in turn ended ~10 seconds before the start of the seizure data segment. The results are combined as one thirty-minute set of plots for the e-data (Fig. 4.1), f-data (Fig. 4.2), g-data (Fig. 4.3), and h-data (Fig. 4.4), with gaps in the analysis to indicate where one dataset ends and the next dataset begins. In particular, the data from 10-590s is the non-seizure epoch with large amplitude signals at 520-600s from chewing and drinking. The data from 610-1190s is the (transition) period immediately before seizure. The data from 1210-1790s includes the seizure and post-ictal phases. The various measures were obtained for every analysis-window, and the resulting values were plotted at the center of the 20-second analysis-window.

Each plot in Figs. 4.1 - 4.4 for Example I displays the analysis-window-centered measure as a solid line. The dashed line (- - -) in each figure is the average value of the measure (from Eq. 6) over an 11-point averaging-window, plotted at the central (sixth) point of the averaging window. The dotted line (. . .) in each figure is the corresponding sample standard deviation over this 11-point averaging-window (from Eq. 9), also plotted at the central point of the averaging-window. The scale length (L_0) was fixed at ~1.4 times the absolute average deviation, as obtained by averaging over the complete non-seizure e-data, and was used in all the analyses as the reference scale length for all three data epochs. Smaller values for this scale length caused numerical problems in the determinations of the correlation dimension and the Kolmogorov entropy; larger values limited the resolution of the nonlinear measures.

The clinical seizure in Example I occurred from 53 to 95s in the (third) seizure epoch (1253 to 1295s in Figs. 4.1-4.4). Rhythmic convulsions began at 1295s, and post-ictal features appeared at 1314s. Table 1 shows features in the nonlinear measures that uniquely indicate the

seizure; starred entries (*) denote no clear indicators. Two measures (the peak in Kolmogorov entropy of g-data and the peak in correlation dimension of h-data) show epilepsy onset beginning ~30 seconds before the clinical seizure.

Table 1 Summary of seizure indicators in Example I

Specific measure	e-data	f-data	g-data	h-data
Time per cycle (T_c) (timesteps per cycle)	*	abrupt decrease $T_c < 200$ 1255-1300s	*	*
Entropy (K) (bits/second)	abrupt increase $K > 0.063$ 1230-1350s	abrupt increases $K > 0.008$ 1230-1240s 1270-1275s 1280-1300s	abrupt increase $K > 0.056$ 1220-1340s	abrupt increase $K > 0.016$ 1230-1320s
1st Min. in MIF (M_1) (timesteps)	*	abrupt decrease $M_1 < 85$ 1290-1310s	*	abrupt decrease $M_1 < 20$ 1270-1280s
Correlation dimension (D)	abrupt increase $D > 5$ 1270-1305s	abrupt increase $D > 5.6$ 1340-1345s	abrupt increase $D > 3.2$ 1235-1340s	abrupt increase $D > 2$ 1220-1325s

EXAMPLE II

The dataset designated Example II is from the same patient as Example I, who is a 20-year-old female with a lifelong history of seizures as previously described in Example I. During the seizure designated Example II, the patient is lying in bed, awake with her right upper

extremity in a flexed posture. The EEG shows spike-wave discharges in the left hemisphere, after which the brain waves become very sharp, dominated by high frequency activity and artifacts. The patient showed eye deviation to the right and some head turning to the right, with head jerking also to the right, but without any usual posturing of the right upper extremity. The eye/head turning is preceded by a high-frequency vocalization. After the clinical seizure spontaneously terminated, the EEG shows high amplitude wave slowing and subsequent amplitude suppression. The subject remained awake during the seizure but was poorly responsive.

The results from Example II for channel 13 involved four analyses (e-, f-, g-, and h-data) on one 23-minute dataset that included all three epochs of channel 13 data (epileptic seizure, non-seizure, and transition from non-seizure to seizure). The non-seizure period spanned 10-400s. The transition period occurred over 410-1200s. The seizure began at 1245s and ended at 1290s. The patient was aphasic at 1300s, with head movements and verbalization at 1315s.

The scale length (L_0) was fixed at ~1.0 times the absolute average deviation, as obtained by averaging over the non-seizure e-data, and was used in all the analyses as the reference scale length for all three data epochs. The results were obtained as before, and are plotted for e-data (Fig. 5.1), f-data, (Fig. 5.2), g-data (Fig. 5.3), and h-data (Fig. 5.4). The seizure is indicated clearly by several unique features in the nonlinear measures, as shown in Table 2; starred entries (*) denote no clear indicators. None of these measures show the epilepsy onset before the clinical seizure.

Table 2 Summary of seizure indicators in Example II

Specific measure	e-data	f-data	g-data	h-data
Time per cycle (T_c) (timesteps/cycle)	*	*	abrupt increases $T_c > 24$ 1255-1275s 1290-1300s	abrupt increases $T_c > 62$ 1250-1275s 1290-1300s
Entropy (K) (bits/second)	abrupt increase $K > 0.089$ 1255-1290s	abrupt increase $K > 0.006$ 1270-1330s	abrupt increase $K > 0.1$ 1255-1290s	abrupt increase $K > 0.014$ 1250-1320s
1st Min. in MIF (M_1) (timesteps)	*	abrupt decrease $M_1 < 80$ 1250-1300s	*	*
Correlation dimension (D)	abrupt increase $D > 4$ 1250-1300s	abrupt increase $D > 4.5$ 1280-1300s	abrupt increase $D > 3$ 1240-1310s	abrupt increase $D > 2.5$ 1240-1315s

In Example I and Example II, abrupt increases in both the Kolmogorov entropy and correlation dimension indicate both epileptic seizures, although the seizures are clinically very different, as described further herein. Abrupt decreases in (T_c) number of timesteps per cycle (for f-data) and in (M_1) the first minimum in the mutual information function (for f- and h-data) also indicate the first seizure (Example I). An abrupt decrease in M_1 (f-data) and abrupt increases

in T_c (g- and h-data) mark the second seizure (Example II). These indicators of seizure are summarized in Tables 1 and 2. The difference in seizure indication (T_c) for the two seizures implies that care is needed in cataloging such features.

It has been shown by the foregoing that certain indicative trends such as sudden increases and sudden decreases in time serial sequences of nonlinear measures hereinbefore described are seizure indicators.

By comparing indicative trends in non-linear measures of the patient's brain wave data with known seizure indicators, it can be clearly determined by whether the indicative trends correspond with known seizure indicators whether a seizure is occurring in the patient.

Tables 1 and 2 and Figures 4 and 5 clearly show that epileptic seizures are indicated by a number of trends in nonlinear measures of brain-wave data including the following: an abrupt decrease in the number of timesteps per cycle for f-data **101**; an abrupt increase in the number of timesteps per cycle for g-data **103**; an abrupt increase in the number of timesteps per cycle for h-data **105**; an abrupt increase in the entropy of e-data **107**; an abrupt increase in the entropy of f-data **109**; an abrupt increase in the entropy of g-data **111**; an abrupt increase in the entropy of h-data **113**; an abrupt decrease in the first minimum in the mutual information function for f-data **115**; an abrupt decrease in the first minimum in the mutual information function for h-data **117**; an abrupt increase in the correlation dimension of e-data **119**; an abrupt increase in the correlation dimension of f-data **121**; an abrupt increase in the correlation dimension of g-data **123**; an abrupt increase in the correlation dimension of h-data **125**; and combinations thereof.

While there has been shown and described what are presently considered the preferred embodiments of the invention, it will be obvious to those skilled in the art that various changes and modifications can be made therein without departing from the scope of the inventions defined by the appended claims.

What is claimed is:

(1) A method for automatically detecting an epileptic seizure in a patient comprising the steps of:

(a) providing at least one channel of a patient's raw brain wave data, called e-data, selected from the group consisting of electroencephalogram data and magnetoencephalogram data;

(b) separating the e-data into artifact data, called f-data, and artifact-free data, called g-data, while preventing phase distortions in the data;

(c) processing g-data through a low-pass filter to produce a low-pass-filtered version of g-data, called h-data;

(d) applying at least one nonlinear measure selected from the group consisting of time steps per cycle, kolmogorov entropy, first minimum in the mutual information function, and correlation dimension to at least one type of data selected from the group consisting of e-data, f-data, g-data, and h-data to provide at least one time serial sequence of nonlinear measures, from which at least one indicative trend selected from the group consisting of abrupt increases and abrupt decreases can be determined;

(e) comparing at least one indicative trend with at least one known seizure indicator; and

(f) determining from said comparison whether an epileptic seizure is occurring in the patient.

(2) The method as described in Claim 1 wherein said at least one time serial sequence of nonlinear measures is selected from the group consisting of: time per wave cycle for e-data, time per wave cycle for f-data, time per wave cycle for g-data, time wave per cycle

for h-data, Kolmogorov entropy for e-data, Kolmogorov entropy for f-data, Kolmogorov entropy for g-data, Kolmogorov entropy for h-data, first minimum in the mutual information function for e-data, first minimum in the mutual information function for f-data, first minimum in the mutual information function for g-data, first minimum in the mutual information function for h-data, correlation dimension for e-data, correlation dimension for f-data, correlation dimension for g-data, correlation dimension for h-data, and combinations thereof.

(3) The method as described in Claim 2 wherein said at least one seizure indicator is selected from the group consisting of: an abrupt decrease in the number of timesteps per cycle for f-data; an abrupt increase in the number of timesteps per cycle for g-data; an abrupt increase in the number of timesteps per cycle for h-data; an abrupt increase in the entropy of e-data; an abrupt increase in the entropy of f -data; an abrupt increase in the entropy of g-data; an abrupt increase in the entropy of h-data; an abrupt decrease in the first minimum in the mutual information function for f-data; an abrupt decrease in the first minimum in the mutual information function for h-data; an abrupt increase in the correlation dimension of e-data; an abrupt increase in the correlation dimension of f-data; an abrupt increase in the correlation dimension of g-data; an abrupt increase in the correlation dimension of h-data; and combinations thereof.

(4) The method as described in Claim 1 wherein the e-data is separated into f-data and g-data by use of a zero-phase filter.

(5) The method as described in Claim 1 wherein the low-pass filter is a standard low-pass filter selected from the group consisting of second-order, third-order, and fourth-order low-pass filters at frequencies between about 35 Hz and about 60 Hz.

(6) The method as described in Claim 5 wherein the low-pass filter is a standard fourth-order low-pass filter at about 50 Hz.

(7) Apparatus for automatically detecting an epileptic seizure in a patient comprising:

(a) data provision means for providing at least one channel of a patient's raw brain wave data called e-data selected from the group consisting of electroencephalogram data and magnetoencephalogram data;

(b) separation means for separating e-data into artifact data, called f-data, and artifact-free data, called g-data, while preventing phase distortions in the data, communicably connected to the data provision means;

(c) low-pass filter means for filtering g-data to produce a low-pass filtered version of g-data, called h-data, communicably connected to the separation means;

(d) application means for applying at least one nonlinear measure selected from the group consisting of time steps per cycle, Kolmogorov entropy, first minimum in the mutual information function, and correlation dimension to at least one type of data selected from the group consisting of e-data, f-data, g-data, and h-data to provide at least one time serial sequence of nonlinear measures, from which at least one indicative trend selected from the group consisting of abrupt increases and abrupt decreases can be determined, communicably connected to the low-pass filter means;

(e) comparison means for comparing at least one indicative trend with known siezure indicators, communicably connected to the application means; and

(f) determination means for determining from the comparison whether an epileptic seizure is occurring in the patient, communicably connected to the comparison means.

(8) The apparatus as described in Claim 7 wherein said at least one time serial sequence of

nonlinear measures is selected from the group consisting of: time per wave cycle for e-data, time per wave cycle for f-data, time per wave cycle for g-data, time wave per cycle for h-data, Kolmogorov entropy for e-data, Kolmogorov entropy for f-data, Kolmogorov entropy for g-data, Kolmogorov entropy for h-data, first minimum in the mutual information function for e-data, first minimum in the mutual information function for f-data, first minimum in the mutual information function for g-data, first minimum in the mutual information function for h-data, correlation dimension for e-data, correlation dimension for f-data, correlation dimension for g-data, correlation dimension for h-data, and combinations thereof.

(9) The apparatus as described in Claim 8 wherein said at least one seizure indicator is selected from the group consisting of: an abrupt decrease in the number of timesteps per cycle for f-data; an abrupt increase in the number of timesteps per cycle for g-data; an abrupt increase in the number of timesteps per cycle for h-data; an abrupt increase in the entropy of e-data; an abrupt increase in the entropy of f -data; an abrupt increase in the entropy of g-data; an abrupt increase in the entropy of h-data; an abrupt decrease in the first minimum in the mutual information function for f-data; an abrupt decrease in the first minimum in the mutual information function for h-data; an abrupt increase in the correlation dimension of e-data; an abrupt increase in the correlation dimension of f-data; an abrupt increase in the correlation dimension of g-data; an abrupt increase in the correlation dimension of h-data; and combinations thereof.

(10) The apparatus as described in Claim 7 wherein said separation means comprises a zero-phase filter.

(11) The apparatus as described in Claim 10 wherein said zero-phase filter is embodied in a programmed integrated circuit semiconductor chip.

(12) The apparatus as described in Claim 7 wherein said low-pass filter means comprises a standard low -pass filter selected from the group consisting of second-order, third-order, and fourth-order low-pass filters at frequencies between about 35 Hz and about 60 Hz.

(13) The apparatus as described in Claim 12 wherein said low-pass filter comprises a standard fourth-order low-pass filter at about 50 Hz.

(14) The apparatus as described in Claim 7 further comprising notification means for providing notification that a seizure is occurring in the patient, said notification means being communicably connected to said determination means.

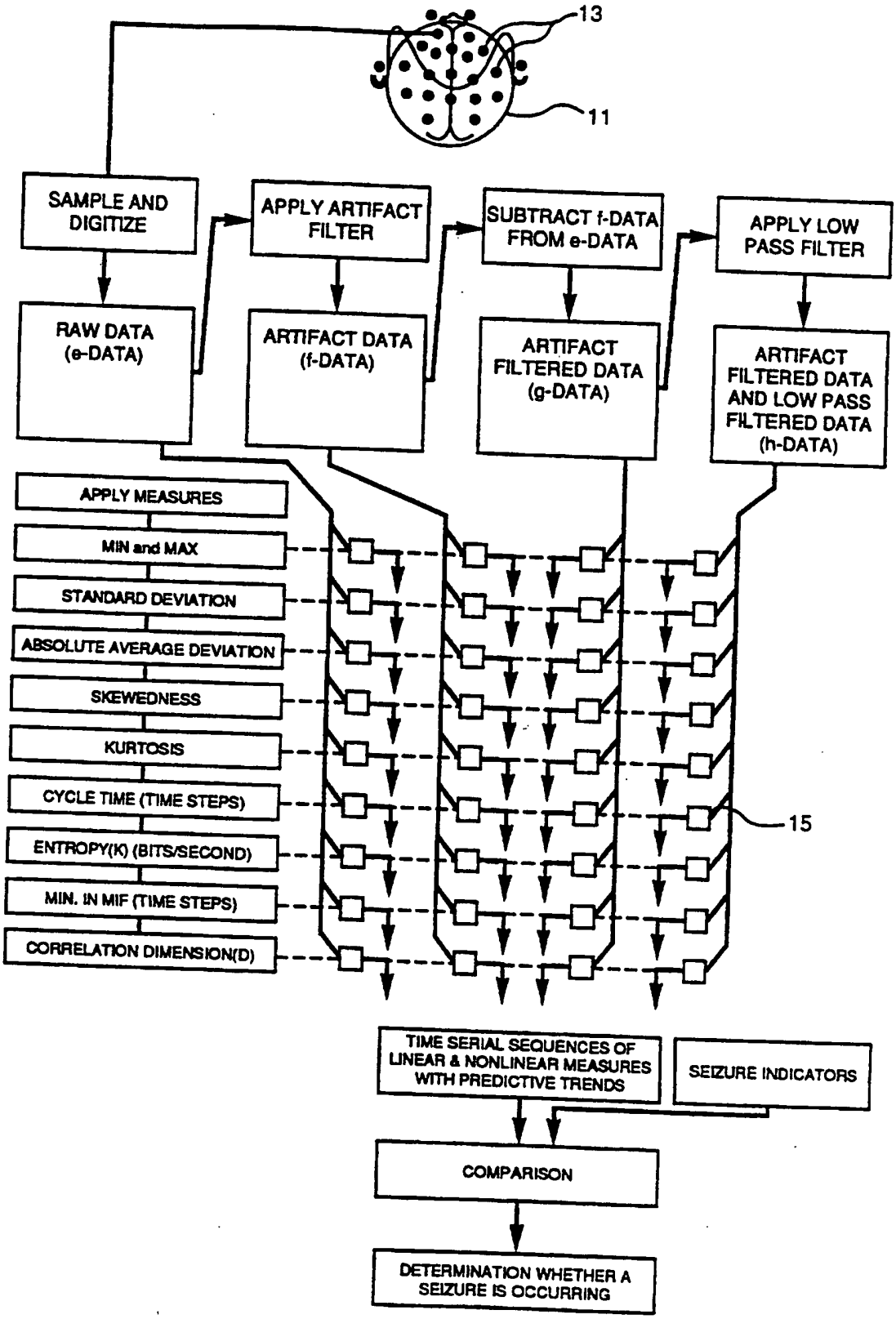
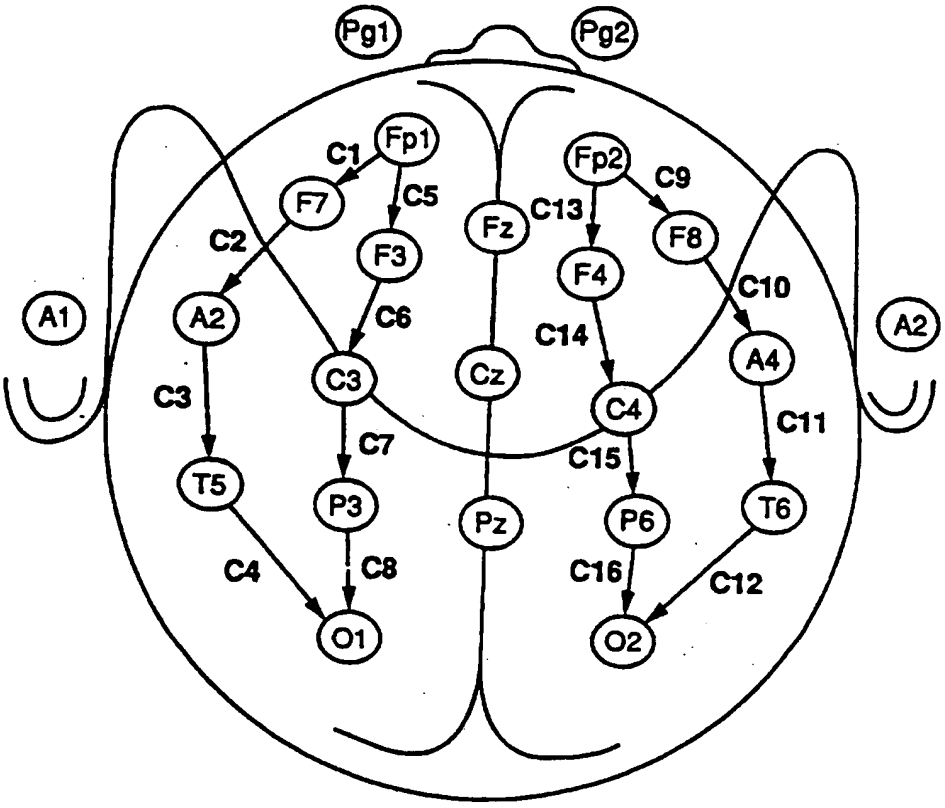

13
11
SAMPLE AND DIGITIZE
APPLY ARTIFACT FILTER
SUBTRACT f-DATA FROM e-DATA
APPLY LOW PASS FILTER
RAW DATA (e-DATA)
ARTIFACT DATA (f-DATA)
ARTIFACT FILTERED DATA (g-DATA)
ARTIFACT FILTERED DATA AND LOW PASS FILTERED DATA (h-DATA)
APPLY MEASURES
MIN and MAX
STANDARD DEVIATION
ABSOLUTE AVERAGE DEVIATION
SKEWEDNESS
KURTOSIS
CYCLE TIME (TIME STEPS)
ENTROPY(K) (BITS/SECOND)
MIN. IN MIF (TIME STEPS)
CORRELATION DIMENSION(D)
15
TIME SERIAL SEQUENCES OF LINEAR & NONLINEAR MEASURES WITH PREDICTIVE TRENDS
SEIZURE INDICATORS
COMPARISON
DETERMINATION WHETHER A SEIZURE IS OCCURRING

Fig. 1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Pg2
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F7
C5
Fz
C13
F8
C2
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A1
A2
C6
C14
A4
A2
C3
Cz
C4
C11
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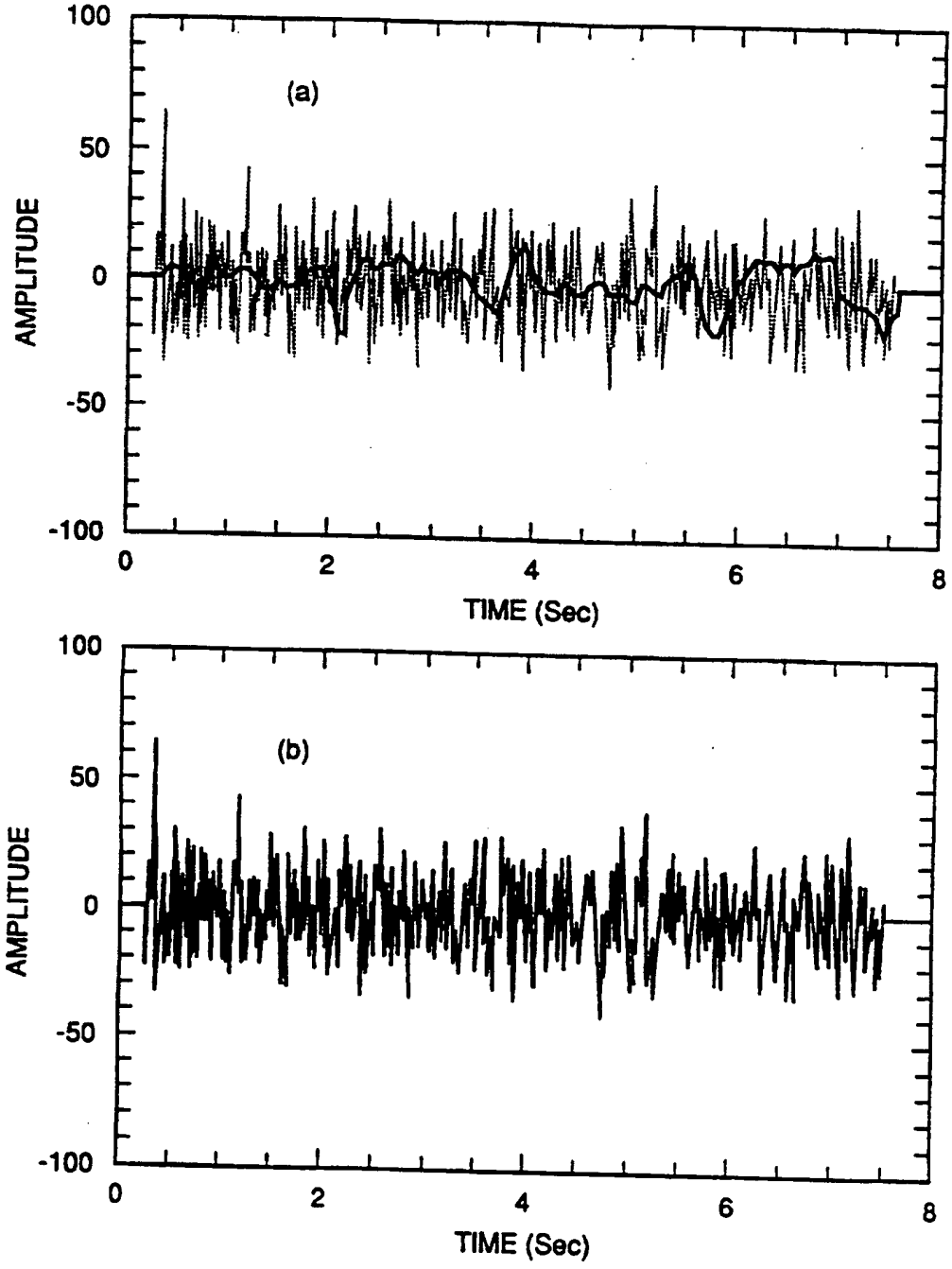
Pz
P6
T6
C4
C8
C16
C12
O1
O2

Fig. 2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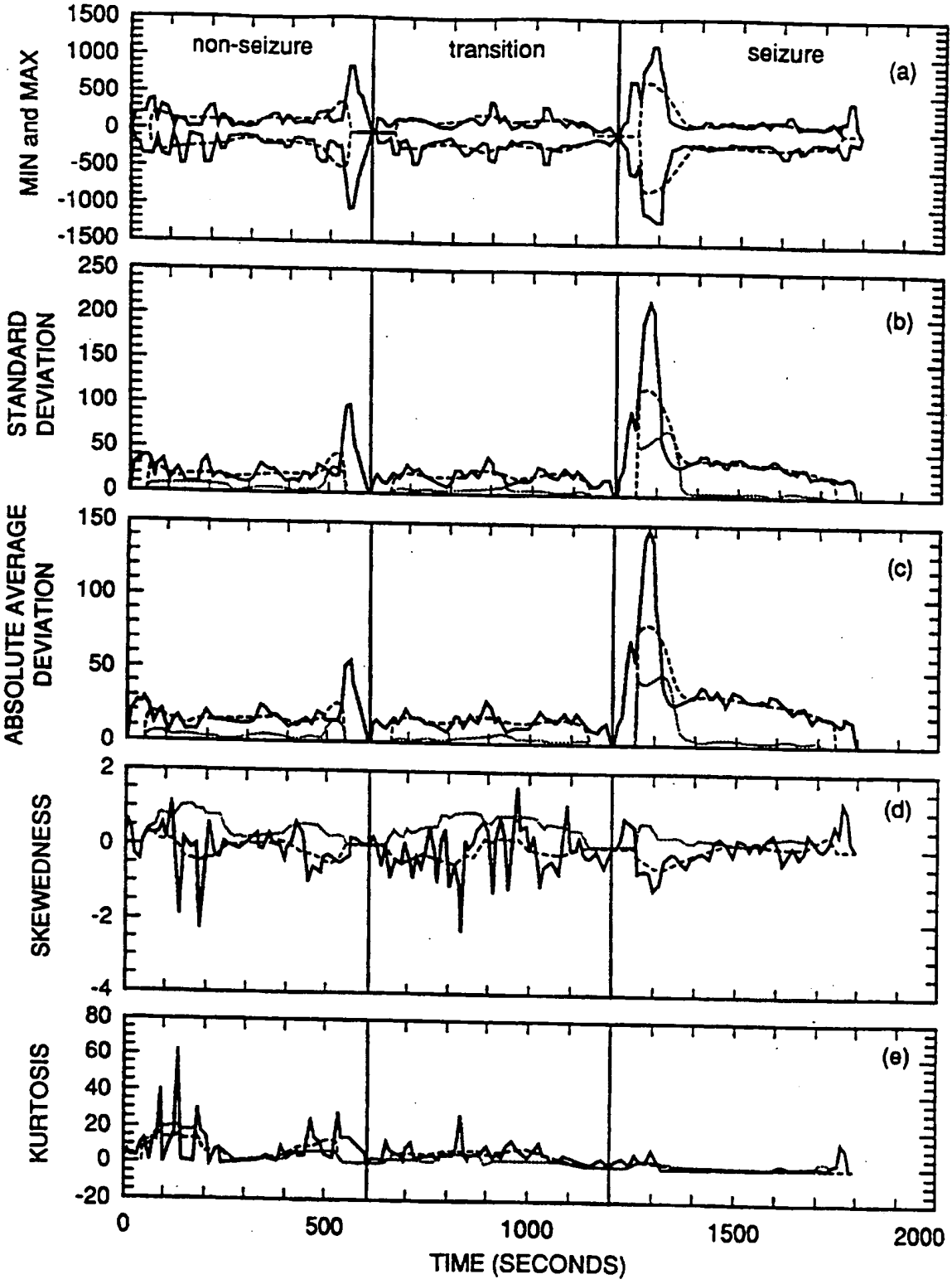
50
0
-50
-100
AMPLITUDE
(a)
0
2
4
6
8
TIME (Sec)
100
50
0
-50
-100
AMPLITUDE
(b)
0
2
4
6
8
TIME (Sec)

Fig. 3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transition
seizure
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MIN and MAX
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1000
500
0
-500
-1000
-1500
(b)
STANDARD DEVIATION
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200
150
100
50
0
(c)
ABSOLUTE AVERAGE DEVIATION
150
100
50
0
(d)
SKEWEDNESS
2
0
-2
-4
(e)
KURTOSIS
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60
40
20
0
-20
0
500
1000
1500
2000
TIME (SECONDS)

Fig. 4.1

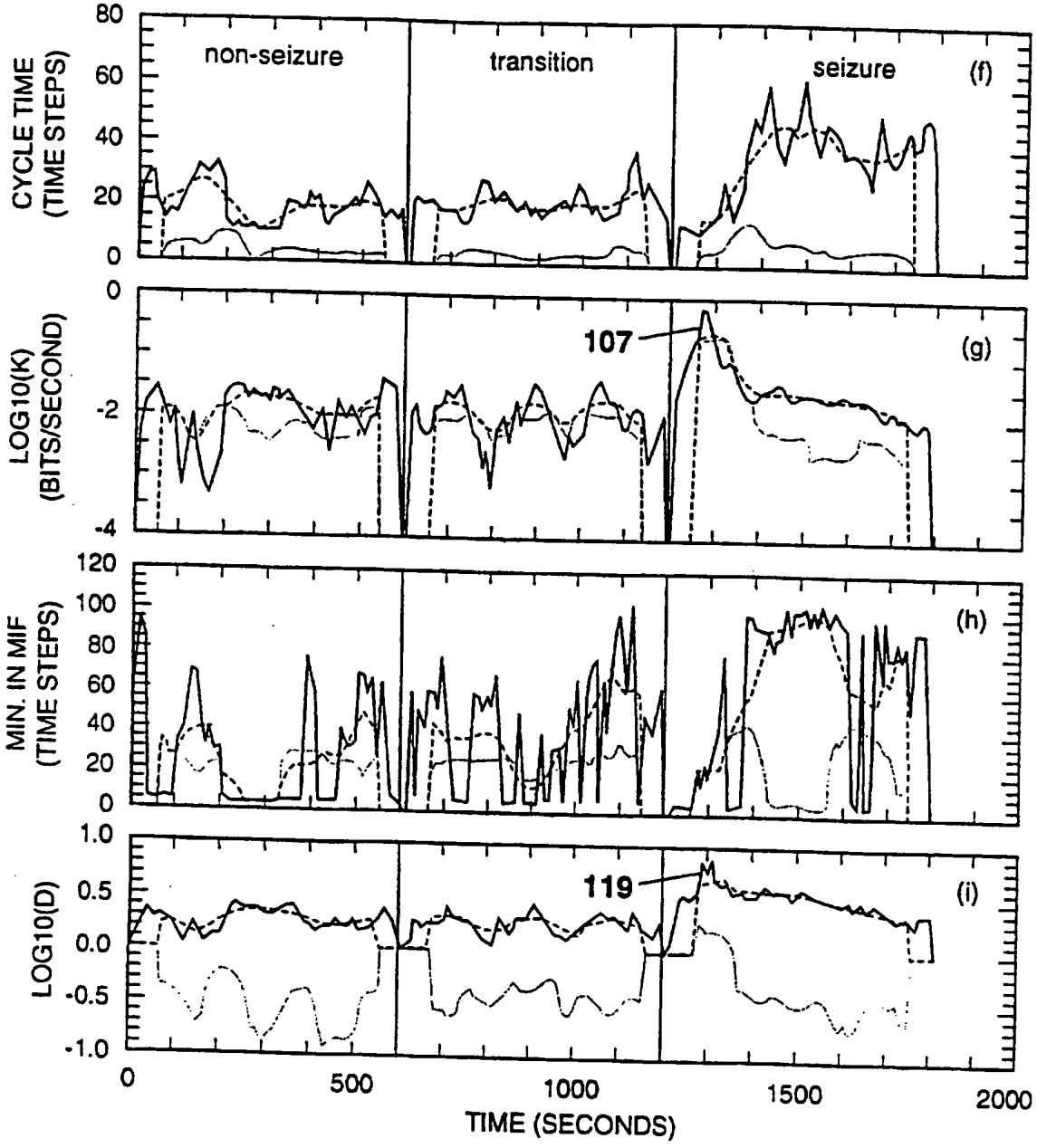
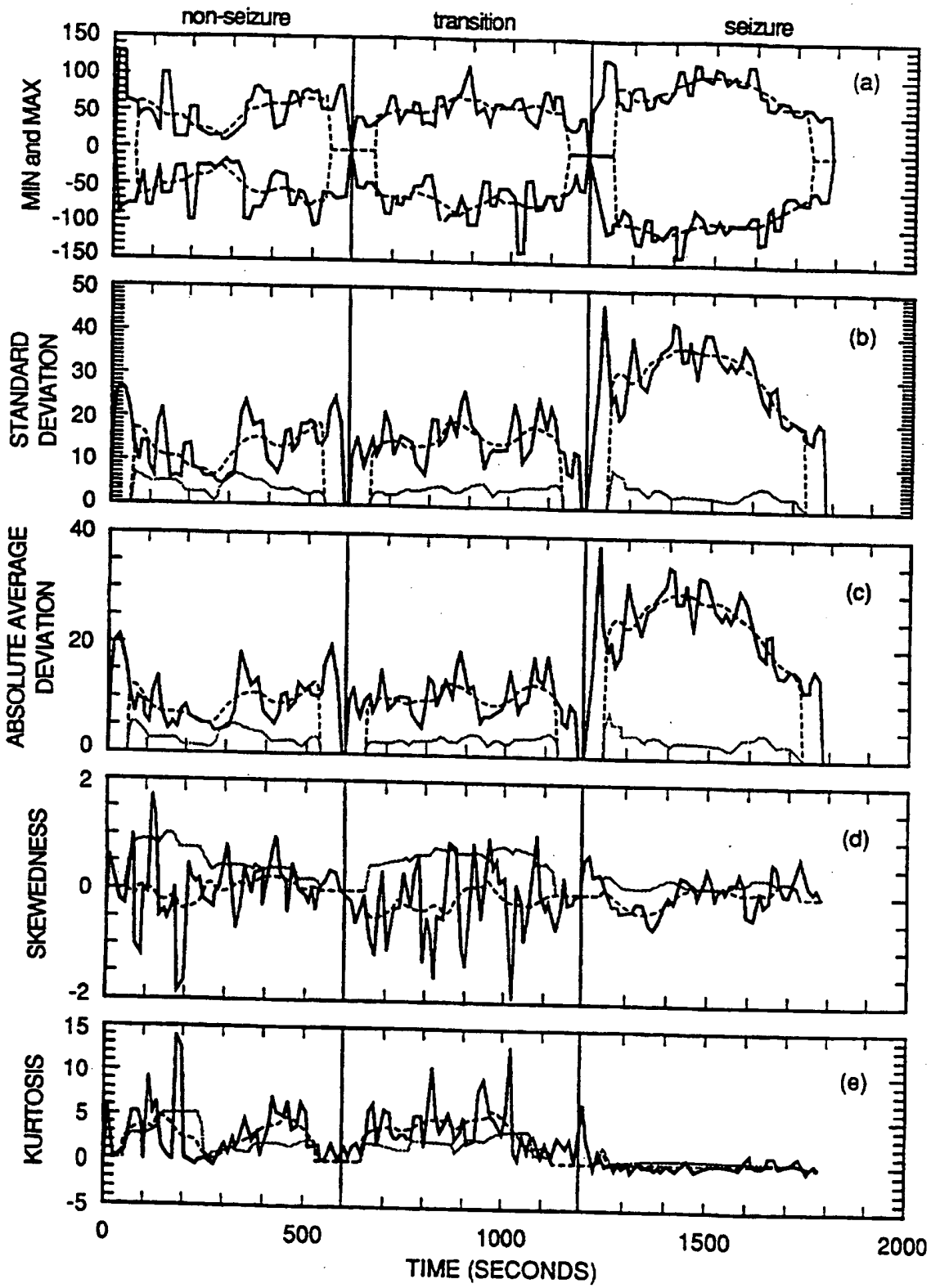


Fig. 4.1 (continued)


non-seizure
transition
seizure
MIN and MAX
150
100
50
0
-50
-100
-150
(a)
STANDARD DEVIATION
50
40
30
20
10
0
(b)
ABSOLUTE AVERAGE DEVIATION
40
20
0
(c)
SKEWEDNESS
2
0
-2
(d)
KURTOSIS
15
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500
1000
1500
2000
TIME (SECONDS)

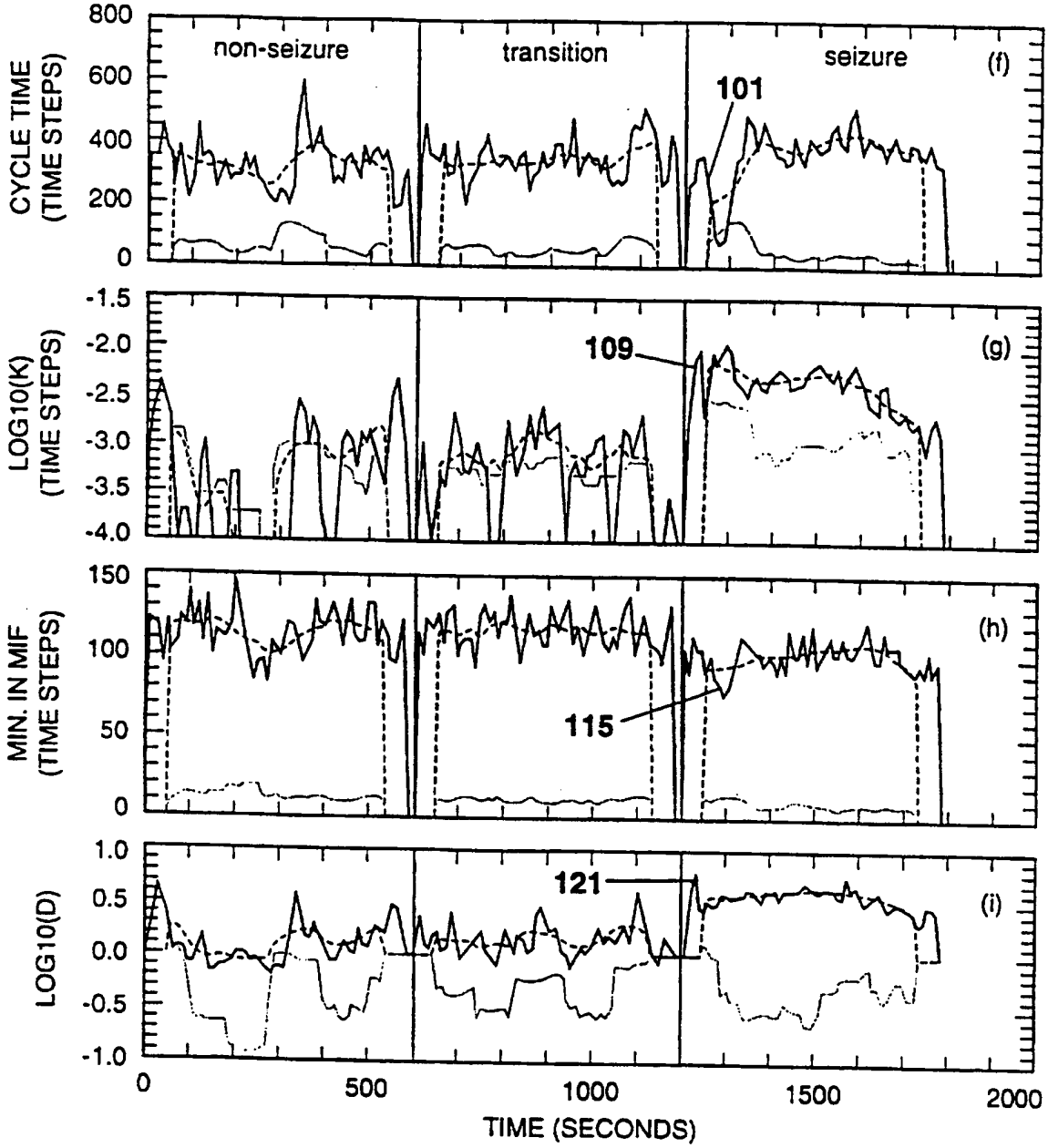

Fig. 4.2 (continued)

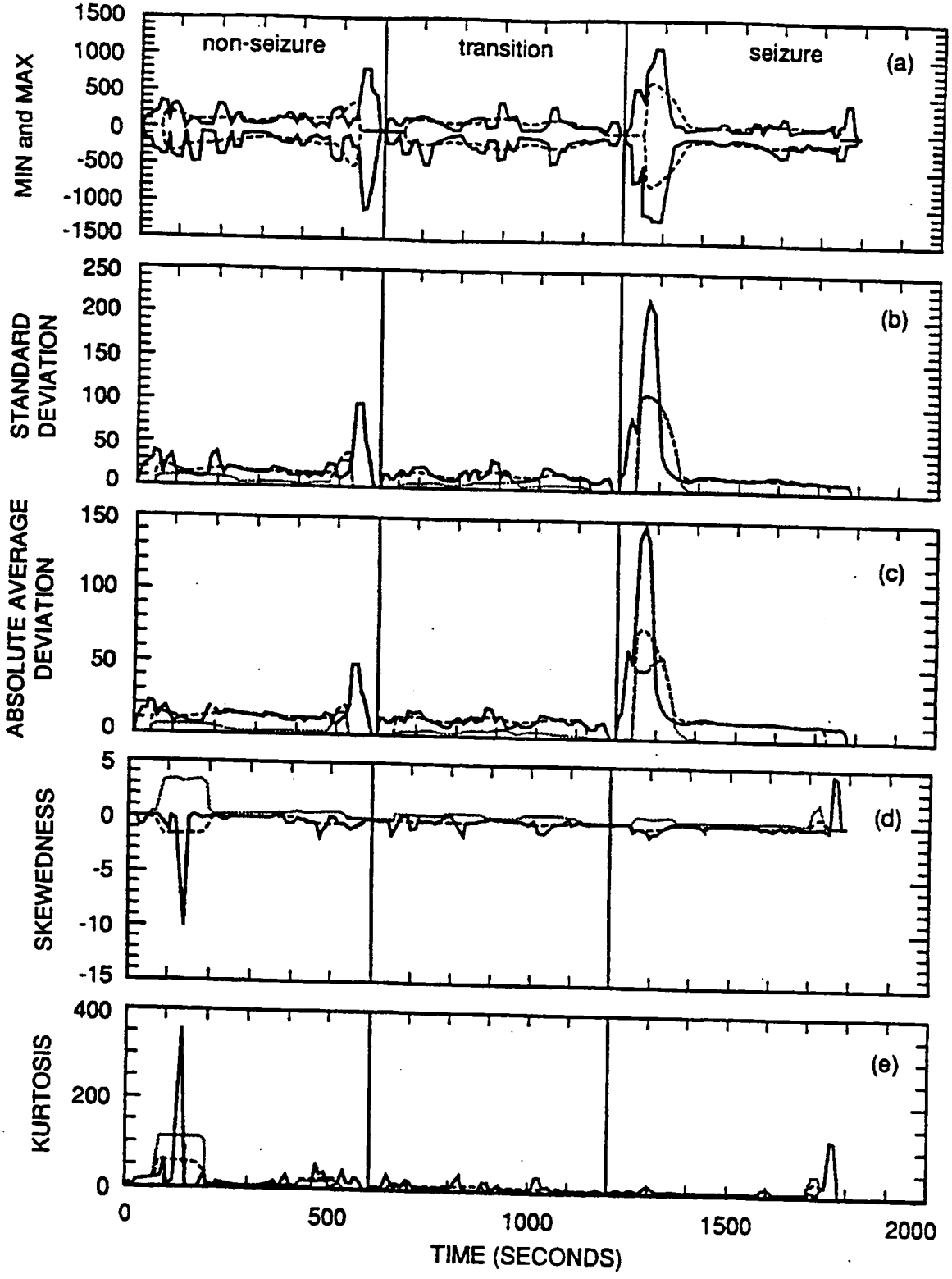
non-seizure
transition
seizure
(a)
MIN and MAX
1500
1000
500
0
-500
-1000
-1500
(b)
STANDARD DEVIATION
250
200
150
100
50
0
(c)
ABSOLUTE AVERAGE DEVIATION
150
100
50
0
(d)
SKEWEDNESS
5
0
-5
-10
-15
(e)
KURTOSIS
400
200
0
0
500
1000
1500
2000
TIME (SECONDS)

Fig. 4.3

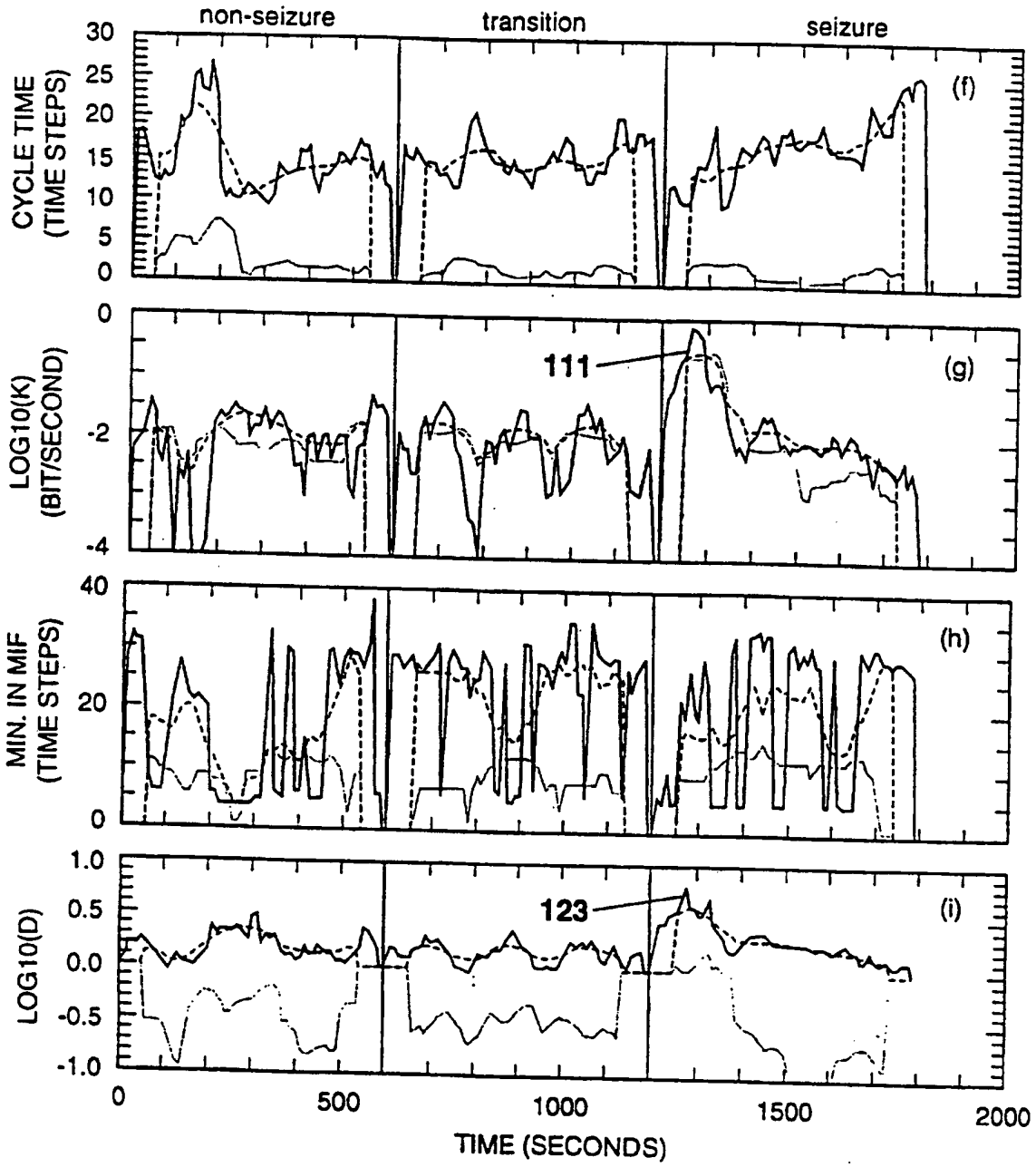

Fig. 4.3 (continued)

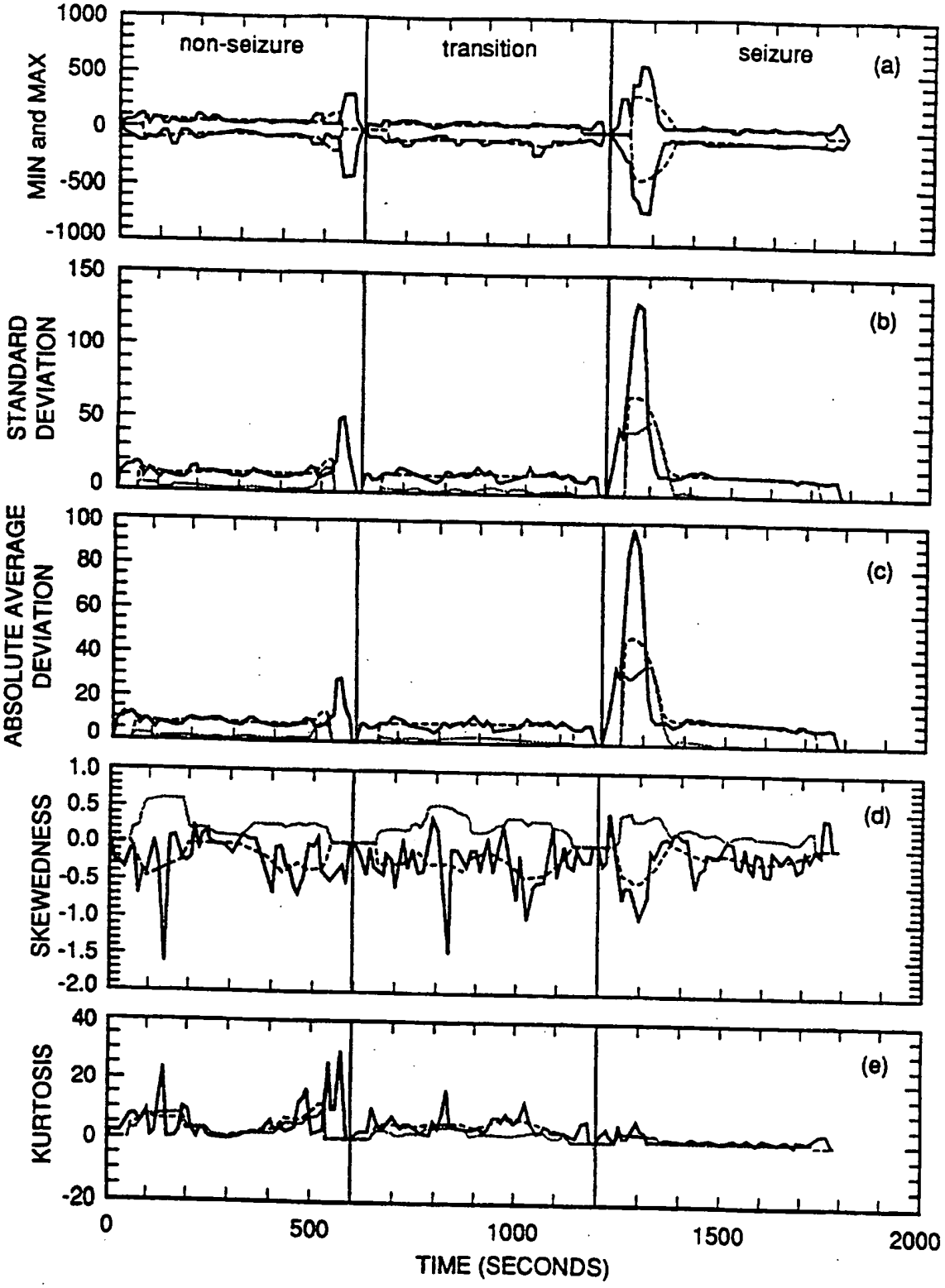
non-seizure
transition
seizure
(a)
MIN and MAX
1000
500
0
-500
-1000
(b)
STANDARD DEVIATION
150
100
50
0
(c)
ABSOLUTE AVERAGE DEVIATION
100
80
60
40
20
0
(d)
SKEWEDNESS
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
(e)
KURTOSIS
40
20
0
-20
0
500
1000
1500
2000
TIME (SECONDS)

Fig. 4.4

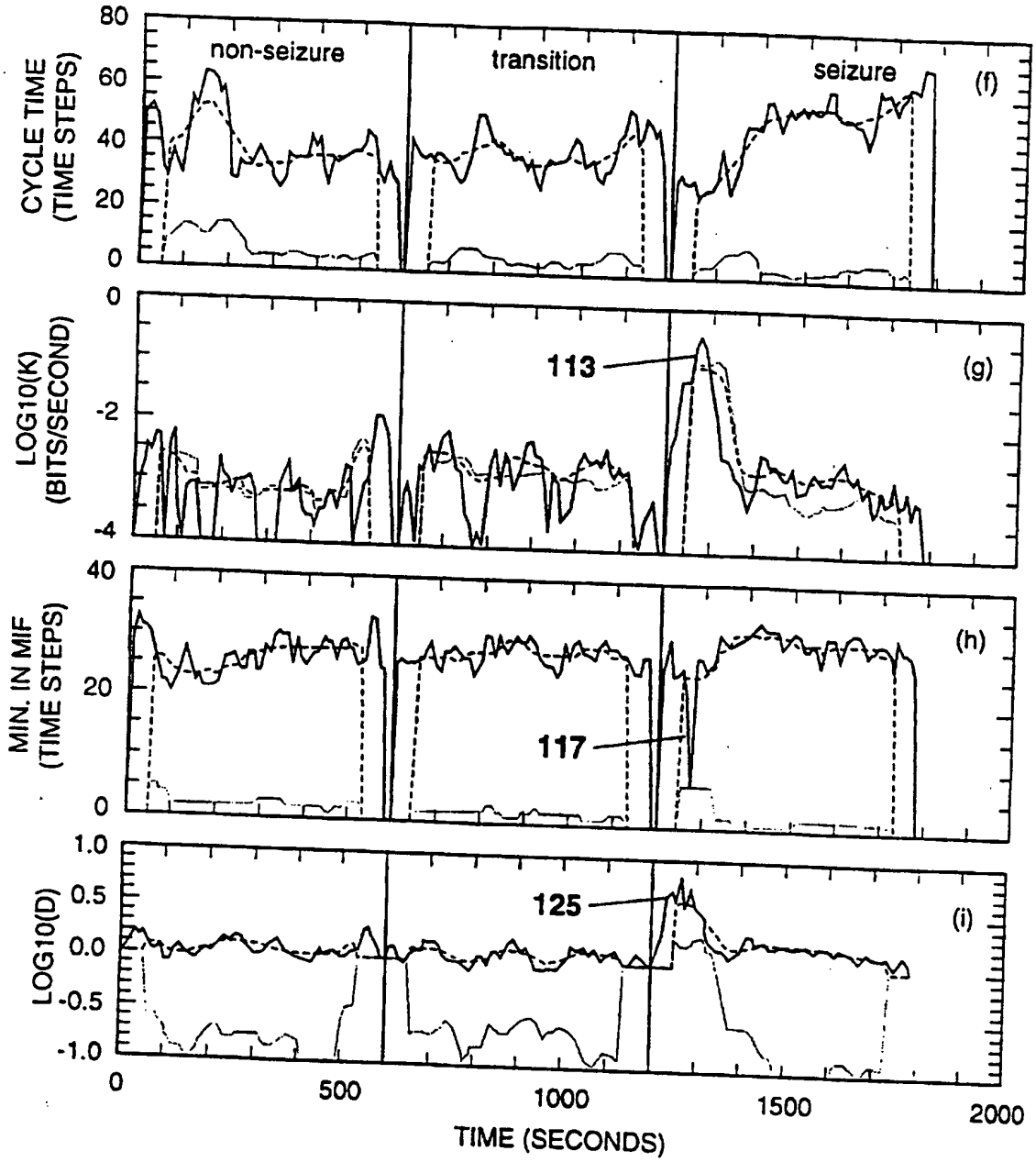

Fig. 4.4 (continued)

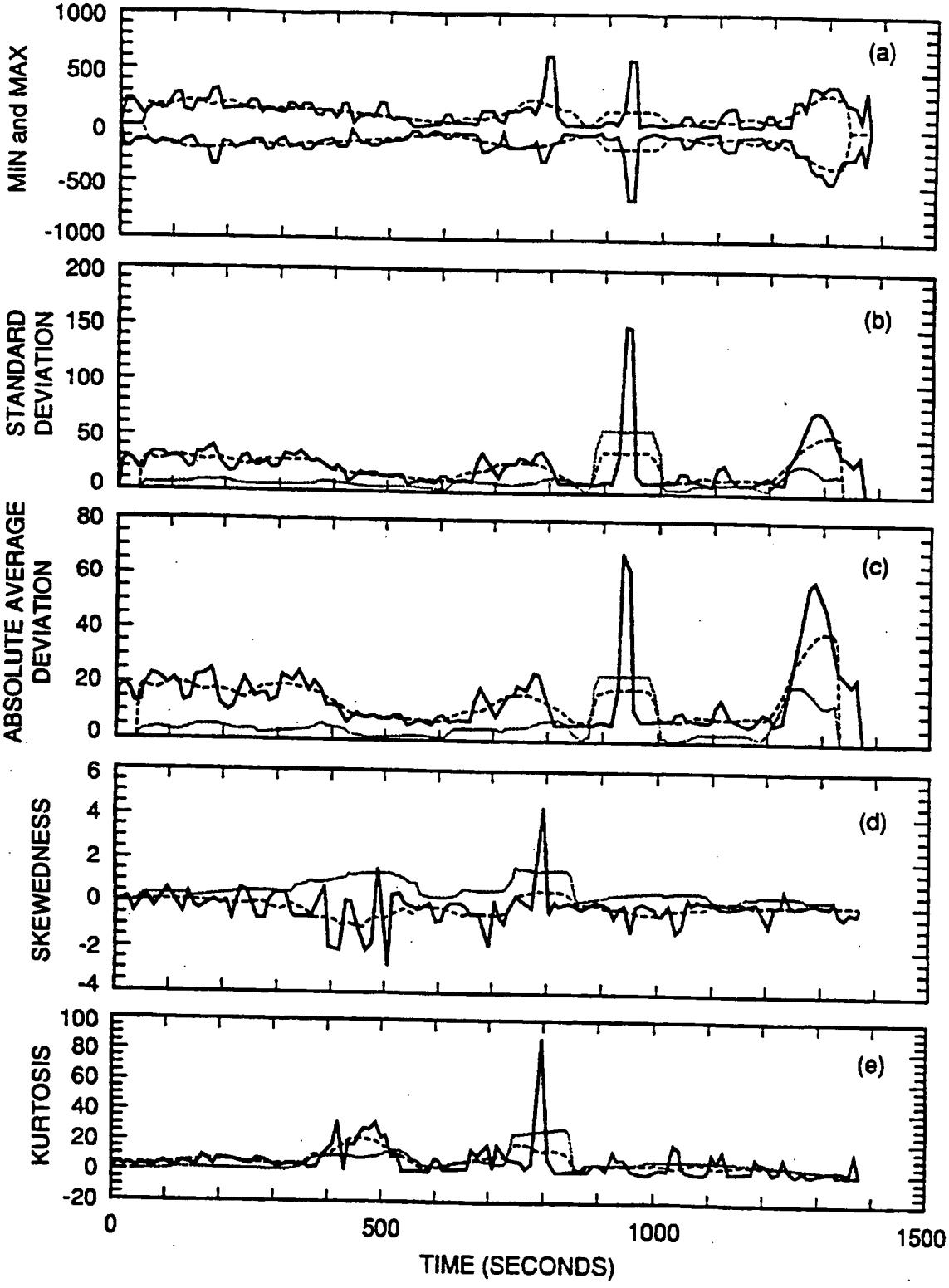
MIN and MAX
1000
500
0
-500
-1000
(a)
STANDARD DEVIATION
200
150
100
50
0
(b)
ABSOLUTE AVERAGE DEVIATION
80
60
40
20
0
(c)
SKEWEDNESS
6
4
2
0
-2
-4
(d)
KURTOSIS
100
80
60
40
20
0
-20
(e)
0
500
1000
1500
TIME (SECONDS)

Fig. 5.1

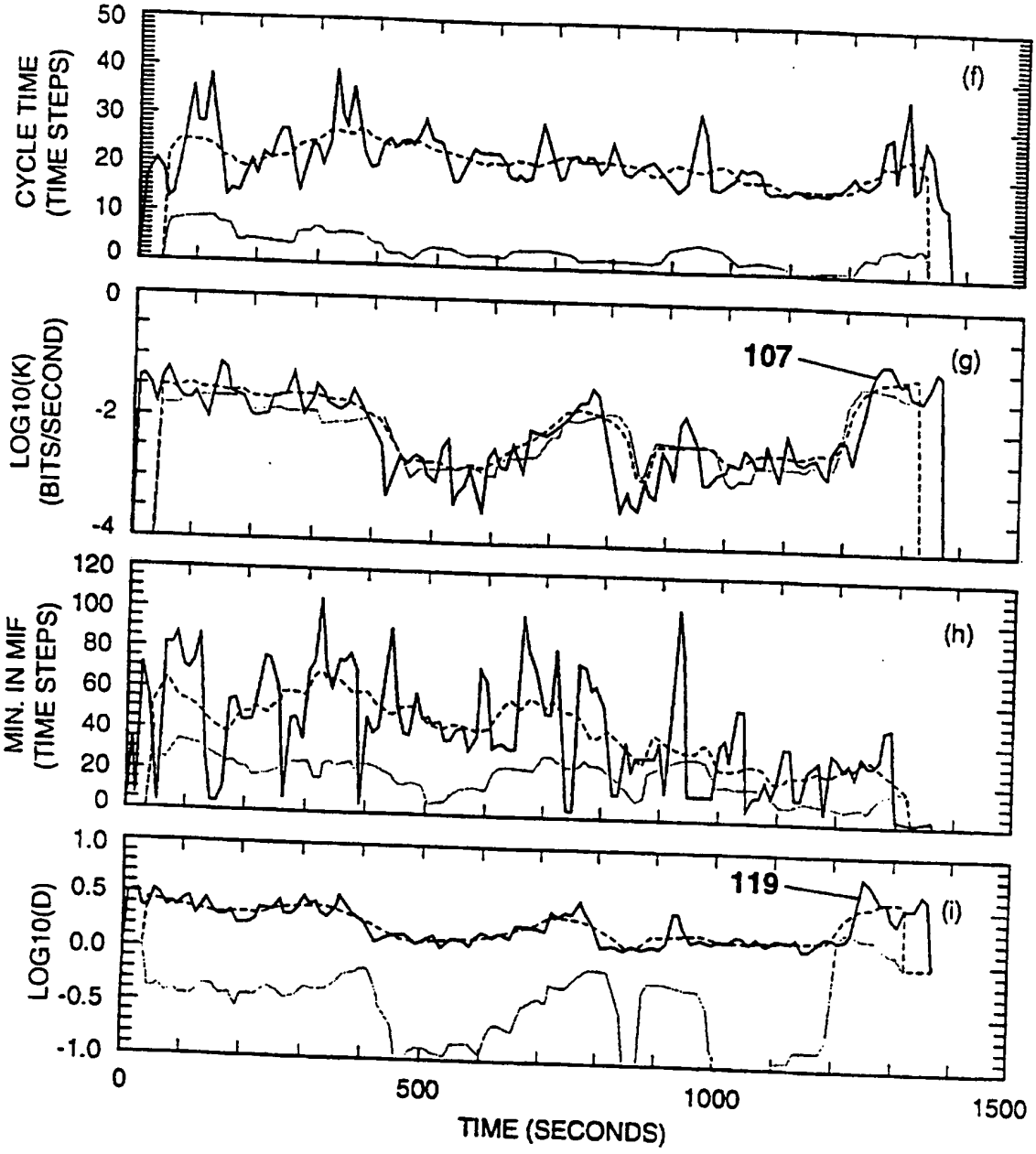

Fig. 5.1 (continued)

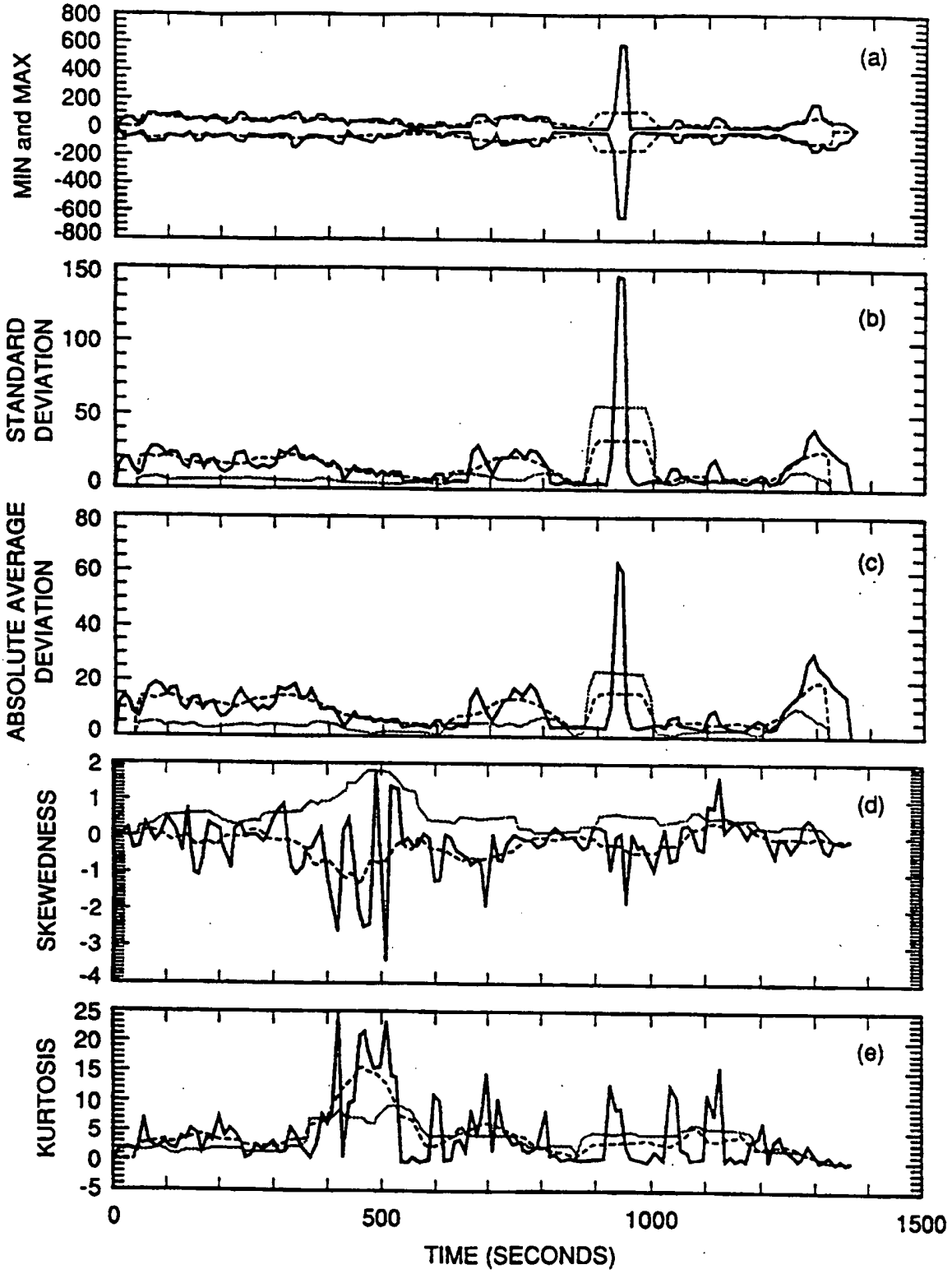
MIN and MAX
800
600
400
200
0
-200
-400
-600
-800
(a)
STANDARD DEVIATION
150
100
50
0
(b)
ABSOLUTE AVERAGE DEVIATION
80
60
40
20
0
(c)
SKEWEDNESS
2
1
0
-1
-2
-3
-4
(d)
KURTOSIS
25
20
15
10
5
0
-5
(e)
0
500
1000
1500
TIME (SECONDS)

Fig. 5.2

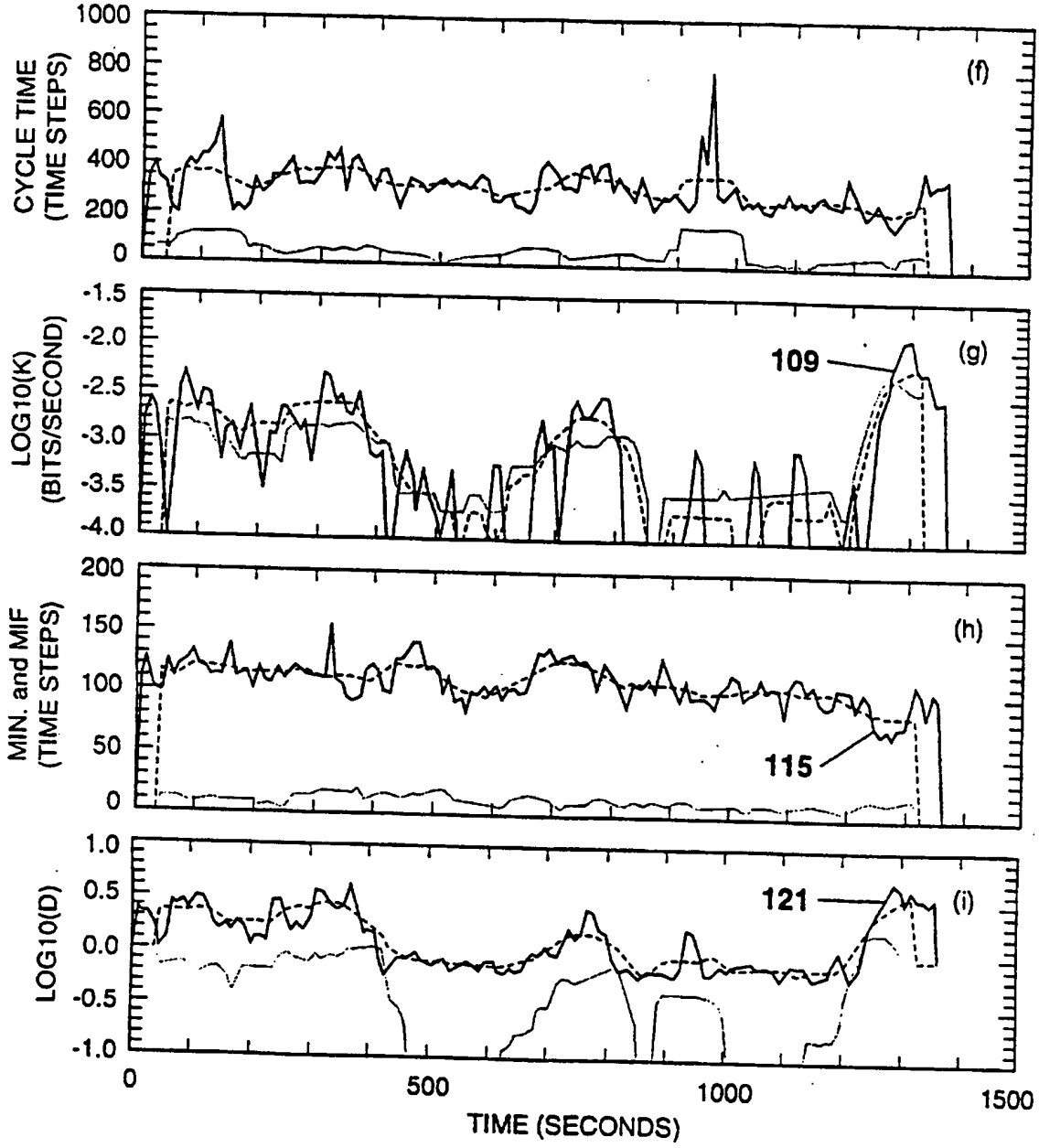

Fig. 5.2 (continued)

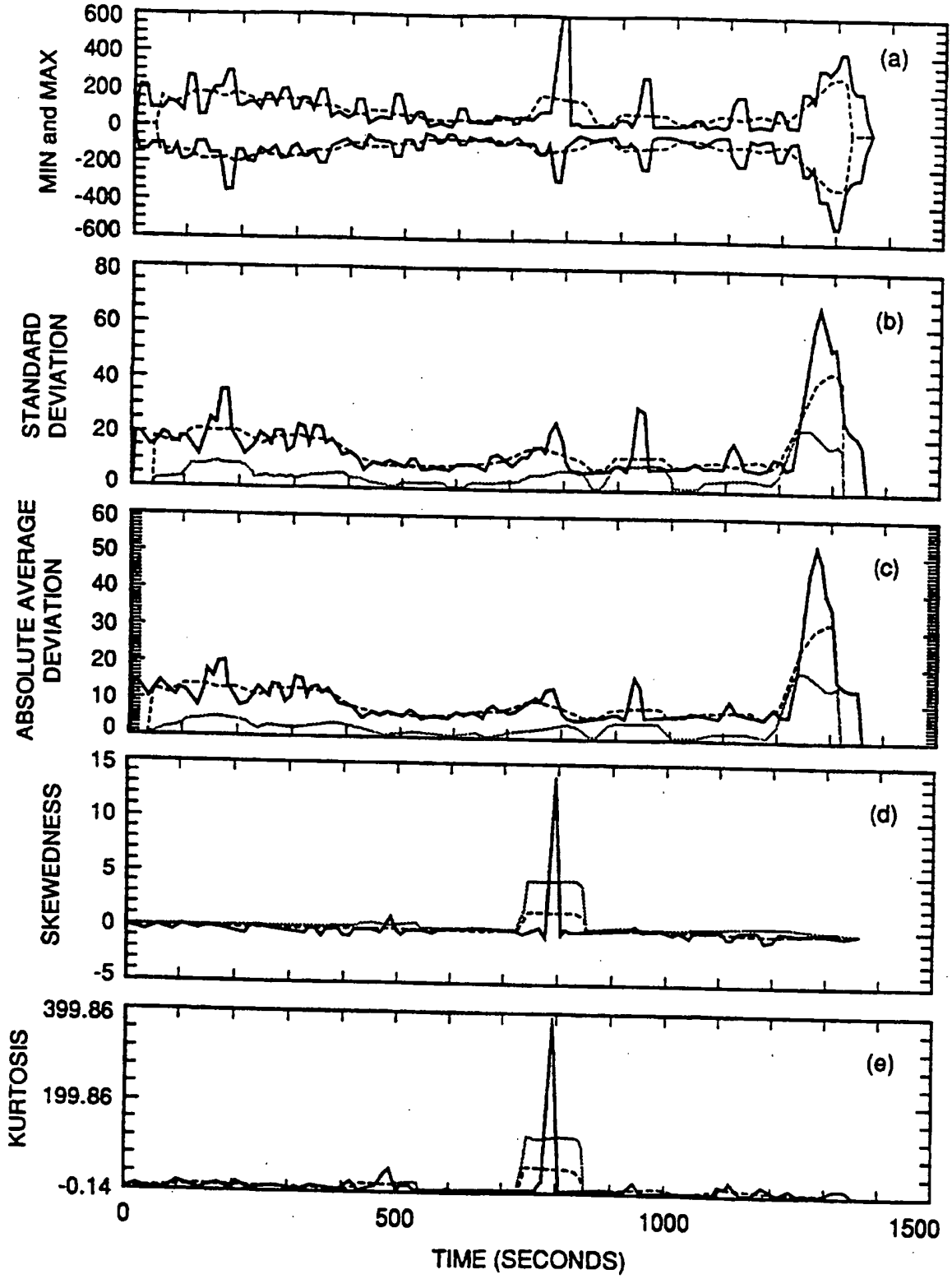
MIN and MAX
600
400
200
0
-200
-400
-600
(a)
STANDARD DEVIATION
80
60
40
20
0
(b)
ABSOLUTE AVERAGE DEVIATION
60
50
40
30
20
10
0
(c)
SKEWEDNESS
15
10
5
0
-5
(d)
KURTOSIS
399.86
199.86
-0.14
(e)
0
500
1000
1500
TIME (SECONDS)

Fig. 5.3

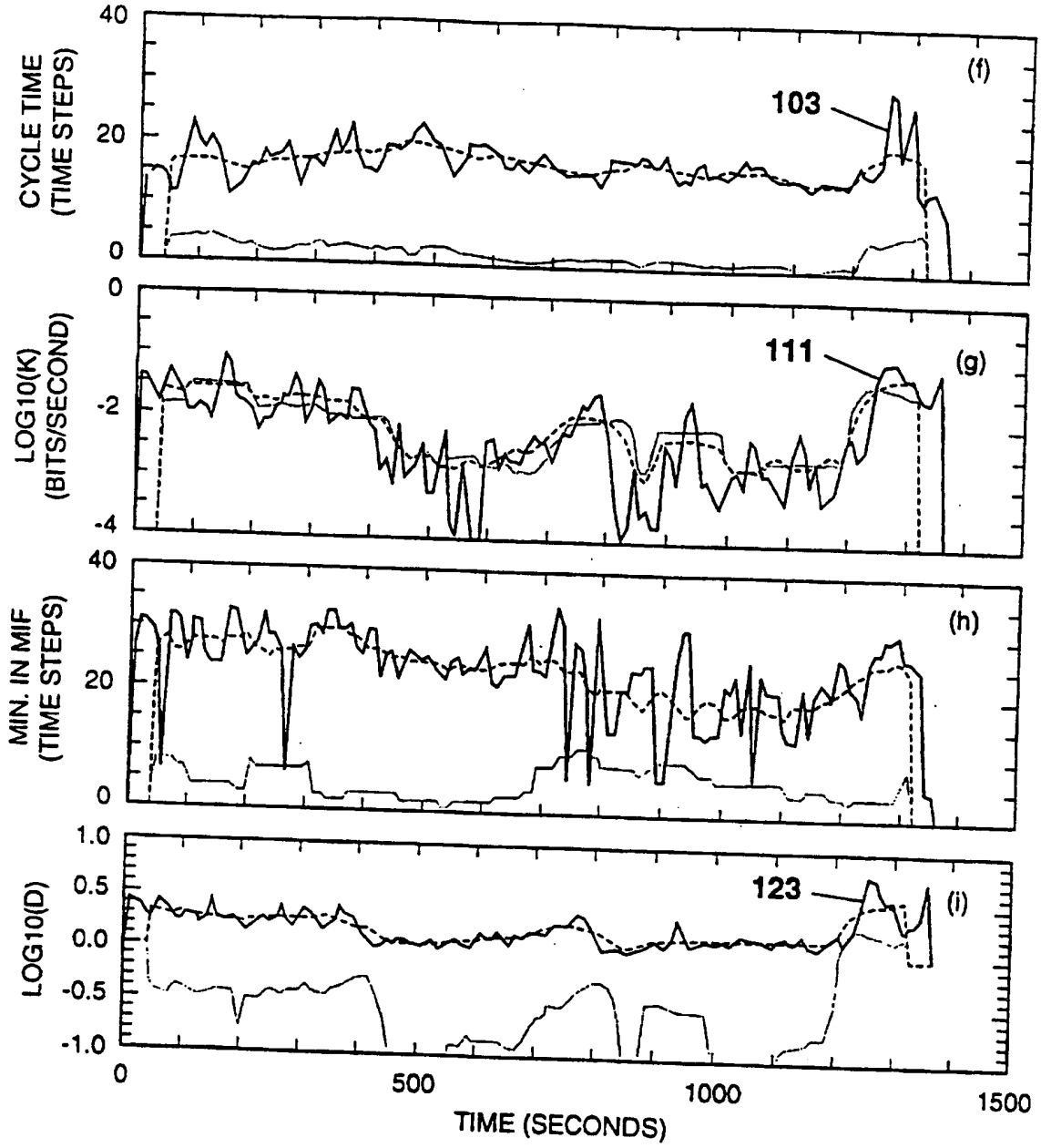

Fig. 5.3 (continued)

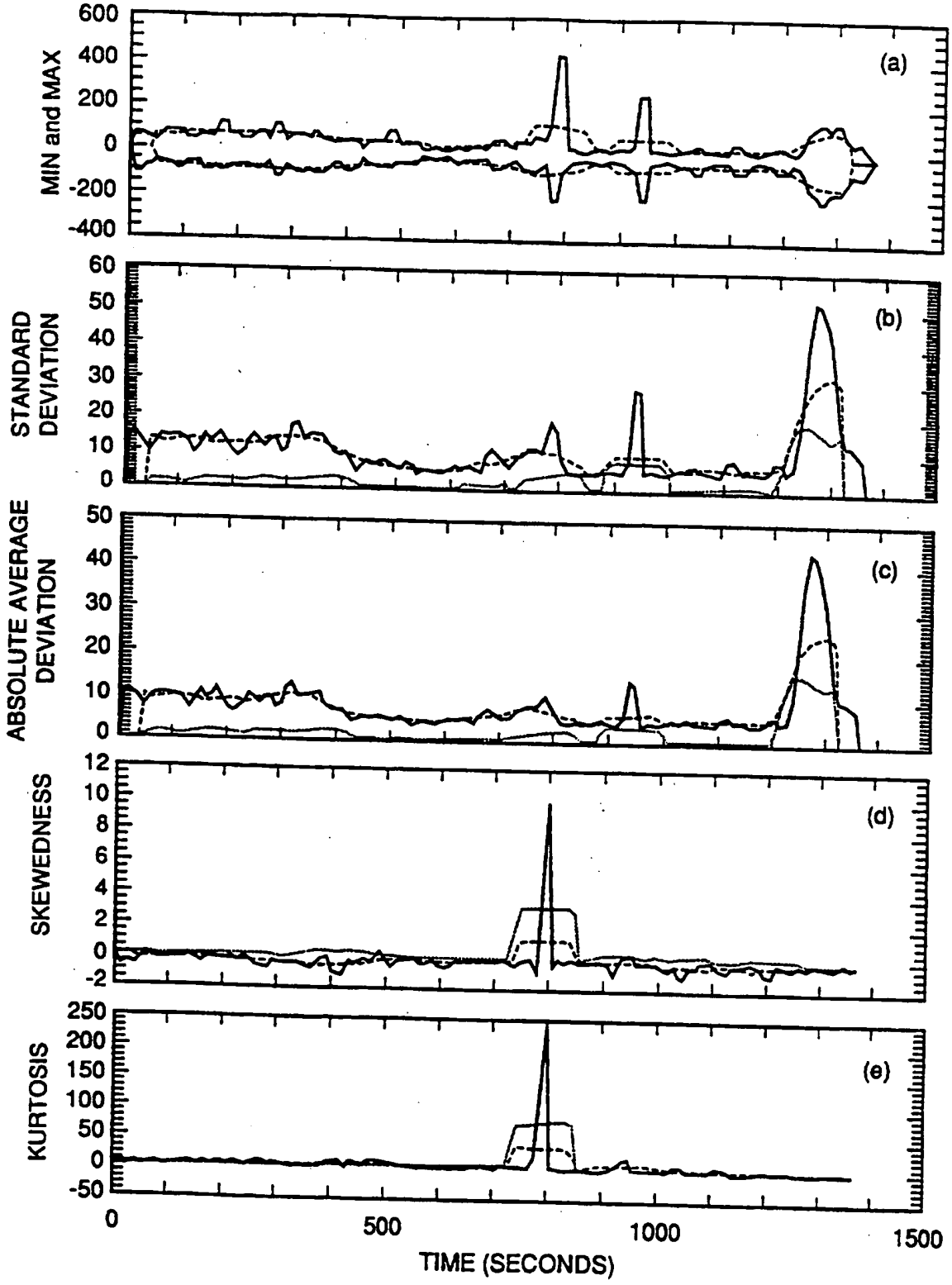
MIN and MAX
600
400
200
0
-200
-400
(a)
STANDARD DEVIATION
60
50
40
30
20
10
0
(b)
ABSOLUTE AVERAGE DEVIATION
50
40
30
20
10
0
(c)
SKEWEDNESS
12
10
8
6
4
2
0
-2
(d)
KURTOSIS
250
200
150
100
50
0
-50
(e)
0
500
1000
1500
TIME (SECONDS)

Fig. 5.4

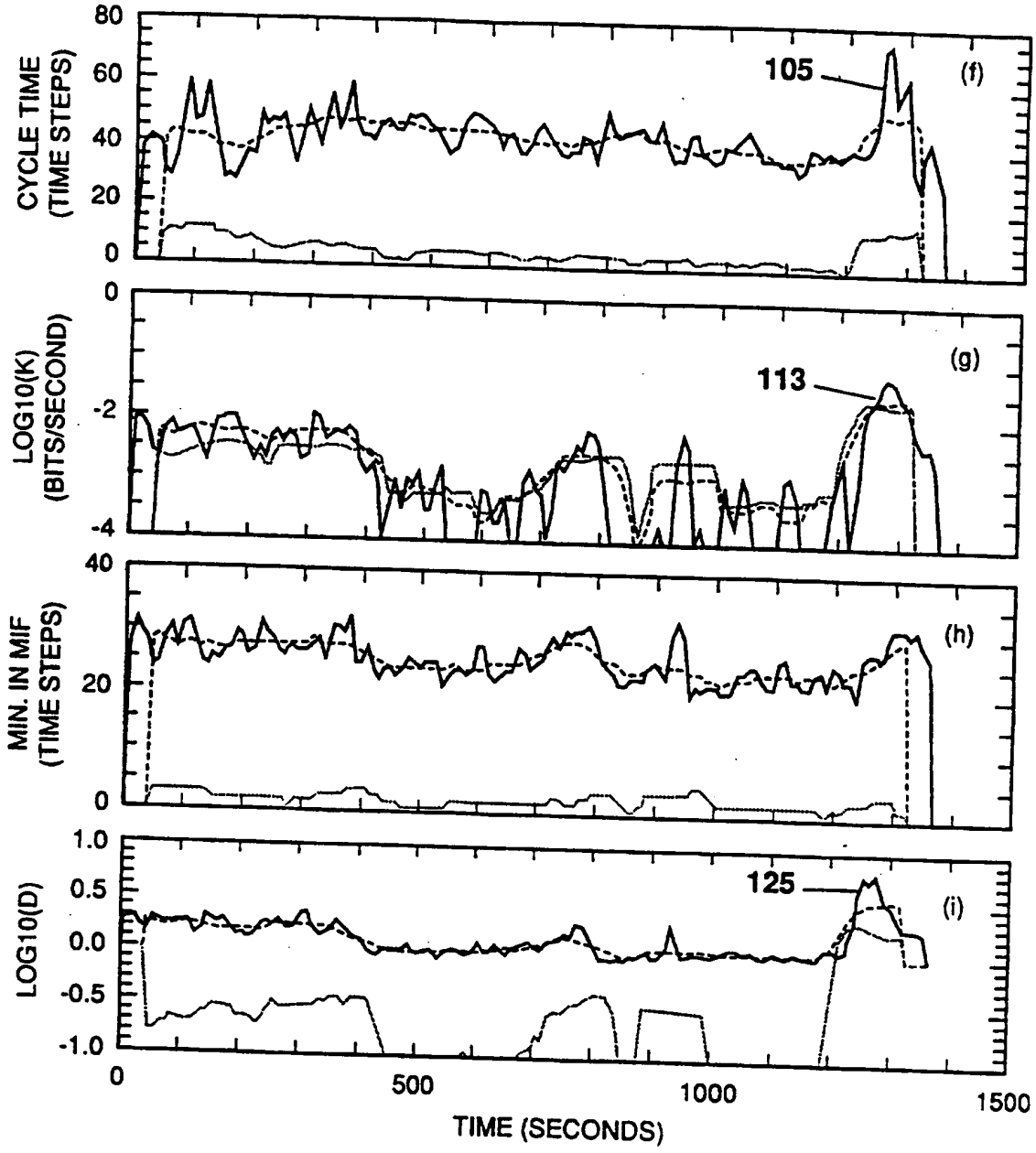

Fig. 5.4 (continued)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/04421

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61B 5/04, 5/0476
US CL : 128/731, 732

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 128/731, 732

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,311,876 A (OLSEN ET AL) 17 May 1994, Fig.1A	7,10-14
A	Pjin, J.P.M., Quantitative Evaluation of EEG Signals in Epilepsy - Nonlinear Associations, Time Delays, and Nonlinear Dynamics, Ph.d. Thesis, University of Amsterdam, 1990, p.70, Fig.20.	1-3 and 7-9

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 MAY 1997	24.06.97
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer C.LAYNO/W.KAMM Telephone No. (703) 308-3694

Form PCT/ISA/210 (second sheet)(July 1992)*